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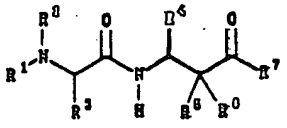
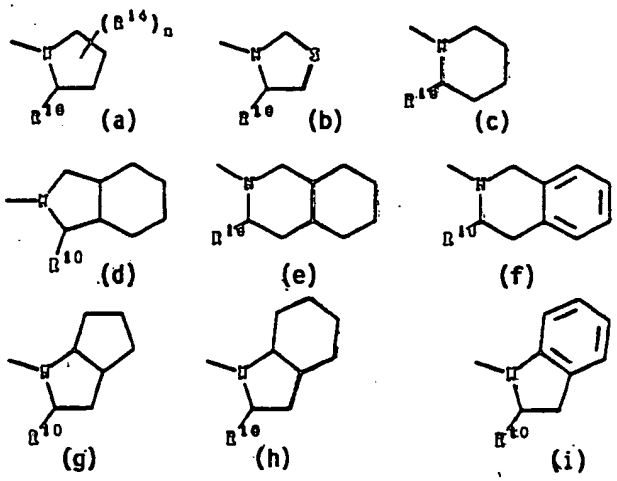


(I)




(57) Abstract

Compounds of formula (I) wherein $R^1$ is alkoxycarbonyl, aralkoxycarbonyl, optionally substituted aralkanoyl, optionally substituted aroyl, optionally substituted heterocyclylcarbonyl, optionally substituted aryloxyalkanoyl, or optionally substituted heterocyclyloxyalkan yl; $R^2$ is hydrogen; $R^3$ is alkyl optionally substituted by hydroxy, carbamoyl, monoalkylcarbamoyl, or dialkylcarbamoyl; $R^4$ is optionally substituted aryl r ptionally substituted aralkyl; $R^5$ is hydrogen; $R^6$ is hydroxy; or $R^5$ and $R^6$ together form oxo, and $R^7$ is selected from the group consisting of (a), (b), (c), (d), (e), (f), (g), (h) and (i), wherein n is 0, 1 or 2; each $R^{14}$ is independently hydroxy, alkyl, alkoxy, or phenyl; and $R^{10}$ is alkoxycarbonyl or optionally substituted monoalkylcarbamoyl; as a single stereoisomer or as a mixture thereof; or as pharmaceutically acceptable salts thereof, are useful in treating disease-states which are alleviated by treatment with an HIV protease inhibitor.

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# Cyclic amides of 3-amino-2-hydroxy-carboxylic acids as HIV-protease inhibitors

**Field of the Invention**

The present invention is directed to compounds, and their pharmaceutically acceptable salts, which inhibit the protease enzyme encoded by the human immunodeficiency virus (HIV), thereby being useful in the prevention of infection by HIV, in the treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). It also relates to pharmaceutical compositions containing the compounds or their pharmaceutically acceptable salts.

## BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system, such as acquired immune deficiency syndrome or AIDS, and degeneration of the central and peripheral nervous system. A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. Interruption of this processing prevents the production of normally infectious virus.

Current treatments for AIDS usually involve the administration of compounds which may inhibit viral DNA synthesis, or which may prevent HIV from penetrating the host cell. None of these current treatments for AIDS have proven to be totally effective in treating and/or reversing the disease. In addition, many of the compounds currently used to treat AIDS cause adverse side effects including low platelet count, renal toxicity and bone marrow cytopenia.

The compounds of formula (I) exhibit the ability to inhibit retroviral proteases, in particular, HIV protease, thereby providing a method for blocking retroviral replication, in particular, HIV replication, and, consequently, a treatment for diseases caused by HIV infection having fewer or no side effects when compared to current treatments.

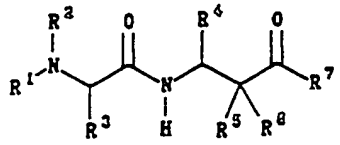
**Related Disclosures**

Peptidyl derivatives are disclosed in several published patent applications as being useful in inhibiting retroviral proteases, for example, European Published Patent Application No. 0 498 680 (Sankyo); European Published Patent Application No. 0 490 667 (Nippon Mining); European Published Patent Application Nos. 0 401 676 and 0 401 675 (Bio-mega); European Published

Patent Application No. 0 356 223 (Merck & Co., Inc.); European Published Patent Application No. 0 342 541 (Abbott Laboratories); European Published Patent Application No. 0 346 847 (Hoffmann-La Roche); and European Published Patent Application No. 0 200 406 (Kissel Pharmaceutical). The design and synthesis of peptidyl derivatives as HIV protease inhibitors is discussed in several research articles, including, but not limited to the following: *Chem. Pharm. Bull* (1991), Vol. 39, No. 9, pp. 2465-2467; *Science* (1990), Vol. 247, pp. 454-456; *Biochemical and Biophysical Research Communications* (1991), Vol. 180, No. 1, pp. 181-185; *Science* (1989), Vol. 246, pp. 1149-1151; *J. Med. Chem.* (1990), Vol. 33, pp. 2687-2689; *Science* (1990), Vol. 248, pp. 358-361; *J. Med. Chem.* (1990), Vol. 33, pp. 1285-1288; *Biochemical and Biophysical Research Communications* (1990), Vol. 169, No. 1, pp. 310-314; *Biochemical and Biophysical Research Communications* (1989), Vol. 163, No. 2, pp. 980-987; and *Biochemical and Biophysical Research Communications* (1989), Vol. 159, No. 2, pp. 420-425.

## SUMMARY OF THE INVENTION

In one aspect, this invention provides compounds of formula (I):



(I)

wherein:

$R^1$ is alkoxycarbonyl, aralkoxycarbonyl, optionally substituted aralkanoyl, optionally substituted aroyl, optionally substituted heterocyclylcarbonyl, optionally substituted aryloxyalkanoyl, optionally substituted carbamoyl or optionally substituted heterocyclyloxyalkanoyl;

$R^2$ is hydrogen;

$R^3$ is alkyl optionally substituted by hydroxy, carbamoyl, monoalkylcarbamoyl, or dialkylcarbamoyl;

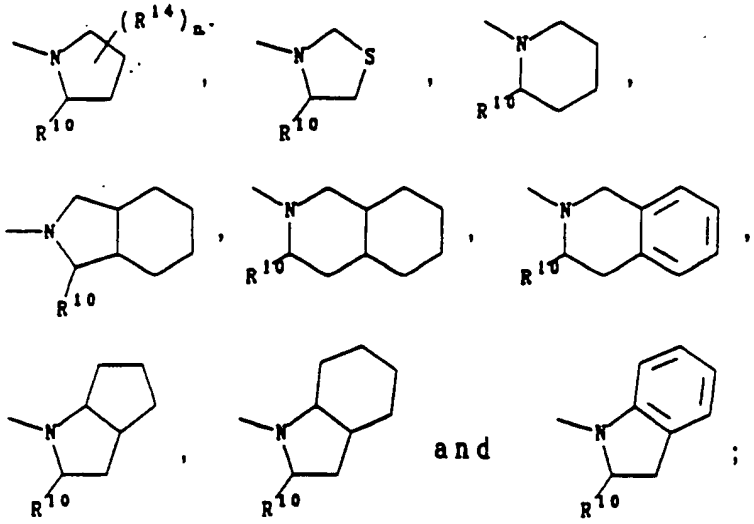
$R^4$ is optionally substituted aryl or optionally substituted aralkyl;

$R^5$ is hydrogen;

$R^6$ is hydroxy; or

$R^5$ and $R^6$ together form oxo; and

$R^7$ is selected from the group consisting of:



wherein

n is 0, 1 or 2;

each $R^{14}$ is independently hydroxy, alkyl, alkoxy or phenyl; and

$R^{10}$ is alkoxycarbonyl or optionally substituted carbamoyl;

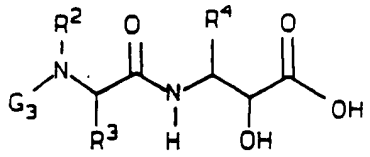
as single stereoisomers or as mixtures thereof; or as pharmaceutically acceptable salts thereof.

In another aspect, this invention provides a method of inhibiting HIV protease activity in a mammal, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) as defined above, as a single stereoisomer, or as a mixture thereof; or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides a pharmaceutical composition useful in inhibiting HIV protease activity in a mammal, which composition comprises a therapeutically effective amount of a compound of formula (I) as defined above, as a single stereoisomer or as a mixture thereof; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

In another aspect, this invention provides processes for the preparation of compounds of formula (I), which processes comprise

a) reacting a compound of the formula

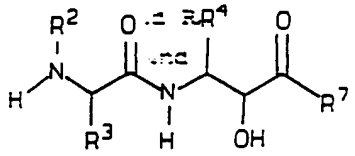


wherein $G_3$ is an amino-protecting group selected from the group consisting of t-butoxycarbonyl, 2-(naphth-1-yl xy)ethanoyl and benzyloxycarbonyl and $R^2$, $R^3$, and $R^4$ are as defined above, with a compound of the formula

$$H - R^7$$

wherein $R^7$ is as defined above, to form a compound of formula (I) wherein $G_3$ is as defined above; or

b) treating a compound of the formula

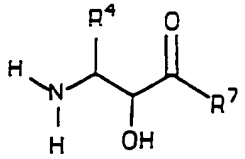


wherein $R^2$, $R^3$, $R^4$, and $R^7$ are as defined above, with a compound of the formula

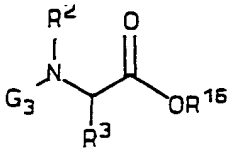
$$R^1 - OH$$

wherein $R^1$ is as defined above, to form a compound of formula (I); or

c) reacting a compound of the formula



wherein $R^4$ and $R^7$ are as defined above, with a compound of the formula



wherein $G_3$, $R^2$, and $R^3$ are as defined above and $R^{16}$ is hydrogen or p-nitrophenyl, to form a compound of formula (I) wherein $G_3$ is as defined above; or

d) oxidizing a compound of formula (I) wherein $R^5$ is hydrogen and $R^6$ is hydroxy, to form a compound of formula (I) wherein $R^5$ and $R^6$ together form oxo; or

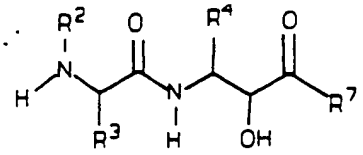
e) converting a compound of formula (I) to a pharaceutically acceptable salt thereof; or

f) converting a pharmaceutically acceptable salt of a compound of formula (I) to the corresponding free compound of formula (I); or

g) converting a pharmaceutically acceptable salt of a compound of formula (I) to another pharmaceutically acceptable salt of a compound of formula (I).

In a further aspect, this invention provides for the preparation of compounds of formula (I), which process, in step a) or c) of the above process, further comprises

a) catalytically hydrogenating a compound of formula (I) wherein $G_3$ is an amino-protecting group selected from the group consisting of t-butoxycarbonyl, 2-(naphth-1-yloxy)ethanoyl and benzyloxycarbonyl and $R^2$, $R^3$, $R^4$, and $R^7$ are as defined above, to form a compound of the formula



followed by

b) treating a compound of formula (L) wherein $R^2$, $R^3$, $R^4$, and $R^7$ are as defined above, with a compound of the formula

$$R^1 - OH$$

wherein $R^1$ is as defined above, to form a compound of formula (I); optionally followed by

c) oxidizing a compound of formula (I) wherein $R^5$ is hydrogen and $R^6$ is hydroxy, to form a compound of formula (I) wherein $R^5$ and $R^6$ together form oxo; or

d) converting a compound of formula (I) to a pharaceutically acceptable salt thereof; or

e) converting a pharmaceutically acceptable salt of a compound of formula (I) to the corresponding free compound of formula (I); or

f) converting a pharmaceutically acceptable salt of a compound of formula (I) to another pharmaceutically acceptable salt of a compound of formula (I).

## DETAILED DESCRIPTION OF THE INVENTION

**Definitions**

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Boc" refers to *t*-butoxycarbonyl.

"CBZ" refers to benzyloxycarbonyl (carbobenzyloxy).

"DCC" refers to *N,N'*-dicyclohexylcarbodiimide.

"DMF" refers to *N,N*-dimethylformamide.

"EDCI" refers to *N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide.

"HOBT" refers to 1-hydroxybenzotriazole.

"Halo" refers to bromo, chloro or fluoro.

"Alkyl" refers to a straight or branched chain monovalent radical consisting solely of carbon and hydrogen, containing no unsaturation and having from one to four carbon atoms, e.g., methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, 1,1-dimethylethyl (*t*-butyl), and the like.

"Alkoxy" refers to a radical of the formula $-OR_a$ wherein $R_a$ is alkyl as defined above, e.g., methoxy, ethoxy, *n*-propoxy, 1-methyleth xy, *n*-butoxy, *t*-butoxy, and the like.

"Alkoxycarbonyl" refers to a radical of the formula $-C(\ )R_b$ wherein $R_b$ is alkoxy as defined above, e.g., meth xycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, and *t*-but xycarb nyl, and the like.

"Aryl" refers to the phenyl or naphthyl radical.

"Aroyl" refers to a radical of the formula $-C(O)R_4$ where $R_4$ is aryl as defined above, e.g., benzoyl or naphthoyl.

"Aralkyl" refers to a radical of the formula $-R_5R_4$ where $R_5$ is alkyl as defined above and $R_4$ is aryl as defined above, e.g., benzyl.

"Aryloxy" refers to a radical of the formula $-OR_4$ where $R_4$ is aryl as defined above, e.g., phenoxy, or naphthyloxy.

"Aralkoxy" refers to a radical of the formula $-OR_6$ where $R_6$ is aralkyl as defined above, e.g., benzyloxy or naphthylmethoxy.

"Aralkanoyl" refers to a radical of the formula $-C(O)R_6$ where $R_6$ is aralkyl as defined above, e.g., phenylethanoyl, phenylpropanoyl, and the like.

"Aralkoxycarbonyl" refers to a radical of the formula $-C(O)OR_6$ is aralkyl as defined above, e.g., benzyloxycarbonyl or naphthylmethoxycarbonyl.

"Aryloxyalkanoyl" refers to a radical of the formula $-C(O)R_5OR_4$ where $R_5$ is alkyl as defined above and $R_4$ is aryl as defined above, e.g., naphth-1-yloxyethanoyl, phenoxyethanoyl, 2-(naphth-2-yloxy)propanoyl, and the like.

"Heterocyclyl" refers to a stable 5- to 7-membered mono- or bicyclic or stable 7- to 10-membered bicyclic heterocyclic ring radical which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and wherein the nitrogen, carbon or sulfur atoms may optionally be oxidized, and the nitrogen atom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic ring radicals is fused to a benzene ring. The heterocyclic ring radical may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic radicals include, but are not limited to, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Preferred heterocyclic radicals for the purposes of this invention are imidazolyl, piperazinyl, pyridyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, and decahydroisoquinolyl.

"Heterocyclylalkyl" refers to a radical of the formula $-R_5R_7$ where $R_5$ is alkyl as defined above and $R_7$ is heterocyclyl as defined above, e.g., quinol-2-ylmethyl, pyrid-2-ylmethyl, imidaz 1-1-ylmethyl, morpholin-4-ylmethyl, 4-methylpiperazin-1-ylmethyl, and the like.

"Heterocyclylcarbonyl" refers to a radical of the formula $-C(O)R_7$ where

$R_r$ is heterocyclyl as defined above, e.g., quinolylcarbonyl, octahydroindolylcarbonyl, and the like.

"Heterocyclyloxyalkanoyl" refers to a radical of the formula $-C(O)R_aOR_r$ where $R_a$ is alkyl as defined above and $R_r$ is heterocyclyl as defined above, e.g., 2-(quinolyl-2-yloxy)ethanoyl, and the like.

"Carbamoyl" refers to the radical $-C(O)NH_2$.

"Monoalkylcarbamoyl" refers to a radical of the formula $-C(O)NH(R_a)$ where $R_a$ is alkyl as defined above, e.g., *N*-methylcarbamoyl, *N*-ethylcarbamoyl, and the like.

"Dialkylcarbamoyl" refers to a radical of the formula $-C(O)N(R_a)_2$ where each $R_a$ is independently alkyl as defined above, e.g., *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N,N*-ethylmethylcarbamoyl, and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

"Optionally substituted aryl" refers to a phenyl or naphthyl group optionally substituted by one or more substituents selected from the group consisting of halo, alkyl, alkoxy, hydroxy, and nitro, e.g., 4-nitrophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 3-hydroxyphenyl, and the like.

"Optionally substituted aralkyl" refers to an aralkyl radical, as defined above, wherein the phenyl or naphthyl group thereof is optionally substituted by one or more substituents selected from the group consisting of halo, alkyl, alkoxy, hydroxy, and nitro, e.g., 4-hydroxybenzyl, 3,5-dichlor - phenylethyl, 6-methoxynaphthylmethyl, and the like.

"Optionally substituted aralkanoyl" refers to aralkanoyl radicals, as defined above, wherein the phenyl or naphthyl group thereof is optionally substituted by one or more substituents selected from group consisting of halo, alkyl, alkoxy, hydroxy, and nitro, e.g., 2-(4-bromonaphth-2-yl)-ethanoyl, 2-(6-methoxynaphth-1-yl)ethanoyl, and the like.

"Optionally substituted aroyl" refers to aroyl radicals, as defined above, wherein the phenyl or naphthyl group thereof is optionally substituted by one or more substituents selected from a group consisting of halo, alkyl, alkoxy, hydroxy and nitro, e.g., 4-bromobenzoyl, 2-(3,5-dichloro-phenyl)ethanoyl, and the like.

"Optionally substituted aryloxyalkanoyl" refers to a aryloxyalkanoyl radical, as defined above, wherein the phenyl or naphthyl group thereof is optionally substituted by ne r more substituents independently selected from the gr up consisting of halo, alkyl, alkoxy, hydroxy, nitro, and heterocyclylalkyl, as defined above. Examples include, but are not limited to 2-(6-bromonaphth-1-yl)oxyethanoyl, 2-(4-methoxy-phenoxy)ethanoyl, 2-(3-(morph lin-4-ylmethyl)phenoxy)ethanoyl, 2-(3-(4-methylpiperazinylmethyl)-phenoxy)ethanoyl, 2-(3-(imidazol-1-ylmethyl)phenoxy)ethanoyl, and the like.

"Optionally substituted heterocyclylcarbonyl" refers to a heterocyclylcarbonyl radical, as defined above, wherein the heterocyclyl group thereof is optionally substituted by one or more substituents selected from the group consisting of halo, alkyl and alkoxy, e.g., 4-bromoquinol-2-ylcarbonyl, and the like.

"Optionally substituted heterocyclyloxyalkanoyl" refers to a heterocyclyloxyalkanoyl radical, as defined above, wherein the heterocyclyl group thereof is optionally substituted by one or more substituents selected from the group consisting of halo, alkyl and alkoxy, e.g., 2-(6-bromoquinol-2-yloxy)ethanoyl, or 2-(8-methoxyquinol-2-yloxy)ethanoyl, and the like.

"Optionally substituted carbamoyl" refers to a carbamoyl radical, as defined above, wherein the nitrogen atom thereof is optionally substituted by an alkyl group, a heterocycyl group, or a heterocyclylalkyl group as defined above. If present, the alkyl group may be optionally substituted by hydroxy, e.g., 1-hydroxy-2-methylprop-2-yl, and the like. Examples include, but are not limited to, *N*-(1-hydroxy-2-methylprop-2-yl)carbamoyl, *N*-methyl-*N*-(pyridin-2-ylmethyl)carbamoyl, and the like.

"Amino-protecting group" as used herein refers to those organic groups intended to protect nitrogen atoms against undesirable reactions during synthetic procedures, and includes, but is not limited to, benzyl, acyl, acetyl, benzyloxycarbonyl (carbobenzyloxy), *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, *t*-butoxycarbonyl, and the like.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, s dium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, trimethamine,

dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline and caffeine.

"Mammal" includes humans and all domestic and wild animals, including, without limitation, cattle, horses, swine, sheep, goats, dogs, cats, and the like.

"Therapeutically effective amount" refers to that amount of a compound of formula (I) which, when administered to a mammal in need thereof, is sufficient to effect treatment, as defined below, for disease-states alleviated by inhibition of HIV protease. The amount of a compound of formula (I) which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease-state and its severity, and the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Treating" or "treatment" as used herein cover the treatment of a disease-state in a mammal, particularly in a human, which disease-state is alleviated by inhibition of HIV protease, e.g., AIDS, ARC, HIV infection, and the like; and include:

(i) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it;

(ii) inhibiting the disease-state, i.e., arresting its development; or

(iii) relieving the disease-state, i.e., causing regression of the disease-state.

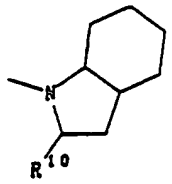
"Stereoisomers" refers to compounds having identical molecular formulae and nature or sequence of bonding but differing in the arrangement of their atoms in space.

The nomenclature used herein is basically a modified form of I.U.P.A.C. nomenclature wherein compounds of the invention are named as derivatives of the $R^7$ moiety, e.g., prolinamide, octahydroindolecarboxamide, decahydroquinolinecarboxamide, octahydroisoindolecarboxamide, and the like.

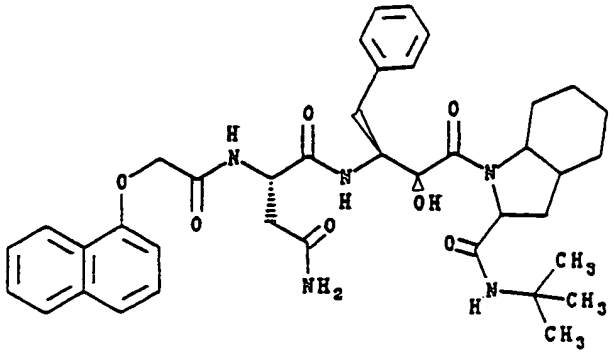
The compounds of formula (I), or their pharmaceutically acceptable salts, have at least two asymmetric carbon atoms in their structure, one to which $R^4$ is attached and the other to which $R^5$ and $R^6$ are attached. In addition, certain $R^7$ substituents may also contain asymmetric carbon atoms. The compounds of formula (I) and their pharmaceutically acceptable salts may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the sc pe of this invention.

When naming the single stere isomers of compounds of formula (I) an absolute descriptor, *R* or *S*, may be assigned to the chiral carbon atoms therein acc rding to the "Sequence Rule" procedure of Cahn, Ingold and Prelog. Stereoisomers of compounds of formula (I) wherein the carb n to which $R^4$ is

attached and the carbon to which $R^5$ and $R^6$ are attached are both in the "*S*" configuration are particularly preferred. In addition, those sections of compounds of formula (I) which includes $R^3$, together with the nitr gen atom and carbonyl group to which it is attached, may define an α-amino acid residue and are named as such. For example, a compound of formula (I) wherein $R^1$ is 2-(naphth-1-yloxy)ethanoyl; $R^2$ is hydrogen; $R^3$ is carbamoylmethyl: $R^4$ is benzyl; $R^5$ is hydrogen; $R^6$ is hydroxy; and $R^7$ is



where $R^{10}$ is *N*-*t*-butylcarbamoyl; i.e., a compound of the following formula:



is named herein as (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-*t*-butylcarboxamido.

Utility and Administration

A. Utility

The compounds of formula (I) are useful in the inhibition of the protease virally encoded by the human deficiency virus (HIV), thereby preventing production of the virus. The compounds of formula (I) are therefore useful in treating disease-states which are alleviated by the inhibition of HIV protease, such as Acquired Immuno Deficiency Syndrome (AIDS) and AIDS Related Complex (ARC). In addition, the compounds of formula (I) prevent infection by HIV by not allowing the virus to replicate within the cells of the body after initial exposure to HIV, e.g., by a blood transfusion, an accidental needle stick, or exposure to patient blood.

B. Testing

The ability of the compounds of f rmula (I) to inhibit HIV protease or the production of HIV can be demonstrated by a variety of *in vitro* assays that are known to those of ordinary skill in the art, such as the *in vitro* assay

described in *Biochem. Biophys. Res. Commun.* (1989), Vol. 164, pp. 955-960, or a modification thereof; or the *in vitro* cell assay described in *Biochem. Pharmacol.* (1987), Vol. 36, pp. 4361-2.

C. General Administration

Administration of the compounds of formula (I), or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally, topically, transdermally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and a compound f formula (I) as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of formula (I), or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. Preferably, the composition will be about 5% to 75% by weight of a compound(s) of formula (I), or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

The preferred route of administration is oral, using a convenient daily dosage regimen which can be adjusted according to the degree of severity of the disease-state to be treated. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of formula (I), or a pharmaceutically acceptable salt thereof, is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like.

Preferably such compositions will take the form of capsule, caplet or tablet and therefore will also contain a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as croscarmellose sodium or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose ether derivatives, and the like.

The compounds of formula (I), or their pharmaceutically acceptable salts, may also be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier that slowly dissolves within the body, e.g., polyoxyethylene glycols and polyethylene glycols (PEG), e.g., PEG 1000 (96%) and PEG 4000 (4%).

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., a compound(s) of formula (I) (about 0.5% to about 20%), or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for treatment of a disease-state alleviated by the inhibition of HIV protease in accordance with the teachings of this invention.

The compounds of formula (I), or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. Generally, a therapeutically effective daily dose is from about 0.14 mg to about 14.3 mg/kg of body weight per day of a compound of formula (I), or a pharmaceutically acceptable salt thereof; preferably, from about 0.7 mg to about 10 mg/kg of body weight per day; and most preferably, from about 1.4 mg to about 7.2 mg/kg of body weight per day. For example, for administration to a 70 kg person, the dosage range would be from about 9.8 mg to about 1.0 gram per day of a compound of formula (I), or a pharmaceutically acceptable salt thereof, preferably from about 50 mg to about 700 mg per day, and most preferably from about 100 mg to about 500 mg per day.

Preferred Embodiments

A preferred group of the compounds of formula (I), as described above in the Summary of the Invention, are those compounds wherein the carbon to which $R^4$ is attached is in the *S*-configuration and the carbon to which $R^5$ and $R^6$ are attached is in the *S*-configuration; and wherein

$R^1$ is aralkoxycarbonyl, optionally substituted aryloxyalkanoyl, optionally substituted carbamoyl or ptionally substituted heterocyclylcarbonyl;

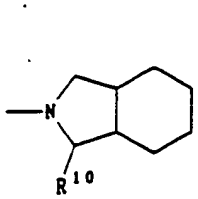
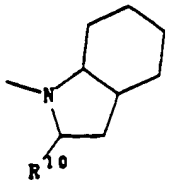
$R^3$ is alkyl optionally substituted by carbamoyl;

$R^4$ is optionally substituted aralkyl;

$R^5$ is hydrogen;

$R^6$ is hydroxy; and

$R^7$ is selected from the group consisting of:

 and 

wherein

$R^{10}$ is monoalkylcarbamoyl.

A preferred subgroup of this group of compounds are those compounds wherein $R^1$ is optionally substituted aryloxyalkanoyl; $R^3$ is 1-methylethyl or methyl substituted by carbamoyl; and $R^4$ is benzyl. Within this subgroup of compounds, more preferred are those compounds wherein $R^1$ is 2-(naphth-1-yloxy)ethanoyl or 2-phenoxyethanoyl.

Another preferred subgroup of compounds are those compounds wherein $R^1$ is optionally substituted heterocyclylcarbonyl; $R^3$ is 1-methylethyl or methyl substituted by carbamoyl; and $R^4$ is benzyl. Within this subgroup, more preferred are those compounds wherein $R^1$ is quinol-2-ylcarbonyl.

Another preferred subgroup of compounds are those compounds wherein $R^1$ is optionally substituted carbamoyl; $R^3$ is 1-methylethyl or methyl substituted by carbamoyl; and $R^4$ is benzyl. Within this subgroup, more preferred compounds are those compounds wherein $R^1$ is *N*-methyl-*N*-(pyridin-2-ylmethyl)carbamoyl.

Presently, the most preferred compounds of formula (I) are the following:

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide;

(1*S*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N*'-t-butylcarboxamide;

(1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N*'-t-butylcarboxamide;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-*iso*-propylcarboxamide;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-phenoxyethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide;

(1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydr isoindole-1-*N*'-t-butylcarboxamide;

(1*S*,3*S*,5*S*)-*N*-[(2*S*,3*S*)-3-(2-(naphth-1-yl xy)ethanoyl-L-asparaginyl)amino-

2-hydroxy-4-phenylbutanoyl)]-2-azabicyclo[3.3.0]octane-3-*N'*-t-butylcarboxamide;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide; and

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(*N*$^{\alpha}$-methyl-*N*$^{\alpha}$-(pyridin-2-ylmethyl)carbamoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide.

Preparation of Compounds of Formula (I)

Compounds of formula (I), as single stereoisomers, or as mixtures thereof, and their pharmaceutical acceptable salts, are peptide derivatives which can be prepared from the constituent α-amino acids. Standard methods for the formation of peptide bonds are further illustrated by M. Bodanszky *et al.*, *The Practice of Peptide Synthesis* (1984), Springer-Verlag; M. Bodanszky, *Principles of Peptide Synthesis* (1984), Springer-Verlag; J.P. Greenstein *et al.*, *Chemistry of the Amino Acids* (1961), Vol. 1-3, John Wiley and Sons Inc.; G.R. Pettit, *Synthetic Peptides* (1970), Vol. 1-2, Van Nostrand Reinhold Company.

Amide couplings used to form the compounds of formula (I) are generally performed by the carbodiimide method with reagents such as dicyclohexylcarbodiimide (DCC), or *N'*-ethyl,*N'*-(3-dimethylaminopropyl)-carbodiimide (EDCI) in the presence of 1-hydroxybenzotriazole (HOBT) in an inert solvent such as dimethylformamide (DMF). Other methods of forming the amide or peptide bond include, but are not limited to, synthetic routes via an acid chloride, acyl azide, mixed anhydride or activated ester such as nitrophenyl ester. Typically, solution phase amide couplings with or without peptide fragments are performed.

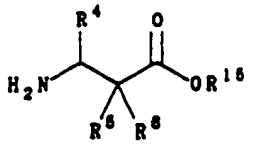
The selection of protecting groups for the terminal amino or carboxy groups of compounds used in the preparation of the compounds of formula (I) is dictated in part by the particular amide or peptide coupling conditions, and in part by the amino acid and/or peptide components involved in the coupling. Amino-protecting groups commonly used include those which are well-known in the art, for example, benzyloxycarbonyl (carbobenzyloxy), *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, t-butoxycarbonyl (Boc), and the like. It is preferred to use either Boc or benzyloxycarbonyl ("CBZ") as the protecting group for the α-amino group because of the relative ease of its removal by mild acids, e.g., by trifluoroacetate acid ("TFA") or hydrochloric acid in ethyl acetate; or by catalytic hydrogenation.

The individual stereoisomers of compounds of formula (I) may be separated from each other by methods known to those of ordinary skill in the art, e.g., by selective crystallization or by chromatography, and/or by the methods cited herein.

When any variable, e.g., $R^3$, $R^{10}$ *r* G, occurs more than once in any substituent or in any formula described herein, its definition on each occurrence, unless specified otherwise, is independent of its definition at every other occurrence. Combinations of substituents and/or variables are

permissible only if such combinations result in stable compounds.

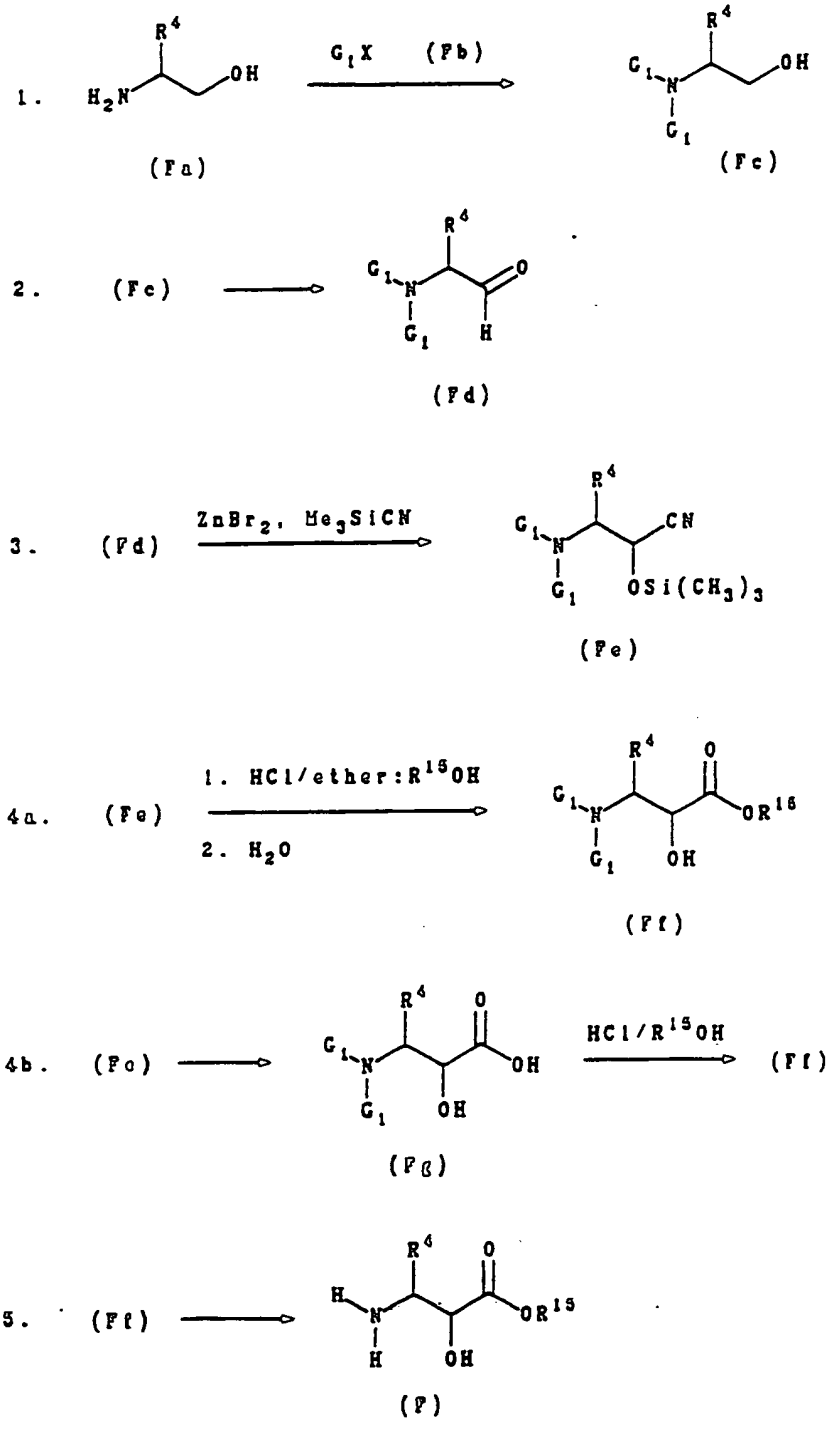
A. Preparation of Starting Materials: Compounds of formula (F). Compounds of the following formula (F);



(F)

where $R^4$ is optionally substituted aryl or optionally substituted aralkyl, preferably benzyl; $R^5$ is hydrogen, $R^6$ is hydroxy, and $R^{15}$ is alkyl are used in the preparation of compounds of formula (I) and are prepared as shown in the following Reaction Scheme 1a where $R^4$ is optionally substituted aryl or optionally substituted aralkyl, preferably benzyl; $R^{15}$ is alkyl, X is brom or chloro and each $G_1$ group is the same and is benzyl:

Reaction Scheme 1a




Compounds of formula (Fa) used in Step 1 of Reaction Scheme 1a, for example, phenylalaninol, tyrosinol and the like, are commercially available, for example, from Aldrich Company, or may be prepared by methods known to those of ordinary skill in the art. Preferably, in Reaction Scheme 1a, compounds of

formula (Fa) are such that the carbon to which the $R^4$ substituent is attached is in the "*S*" configuration.

Compounds of the formula $R^{15}OH$ used in steps 4a and 4b of Reaction Scheme 1a, for example, methanol and ethanol, are commercially available, for example, from Aldrich Company, or may be prepared by methods known to th se of ordinary skill in the art.

Compounds of formula (Fb), for example, benzyl bromide and benzyl chloride, used in step 1 of Reaction Scheme 1a, are commercially available, for example, from Aldrich Company, or may be prepared by methods known to those of ordinary skill in the art.

In general, a compound of formula (F) is prepared by the process described by Reaction Scheme 1a by first treating a compound of formula (Fa) with 2.2 to 2.5 molar equivalents of a compound of formula (Fb) in the presence of a base, preferably potassium carbonate, in refluxing water for a period of 1 to 5 hours, preferably for four hours. The resulting solution is then cooled and the compound of formula (Fc) is then isolated from the solution by conventional isolation techniques, for example, by extraction followed by chromatography (Step 1).

In Step 2 a compound of formula (Fc) in an inert solvent, for example, methylene chloride, is treated with an oxidizing agent, preferably, oxalyl chloride and methyl sulfoxide in an inert solvent, for example, methylene chloride, at initial temperatures of below -60°C. The resulting solution is allowed to warm to room temperature and the corresponding compound of formula (Fd) is then isolated from the solution by conventional isolation techniques, for example, by extraction and chromatography.

Compounds of formula (Fe) are prepared in Step 3 according to the procedure described in *Tetrahedron Letters* (1988), pp. 3295-3298, by M.T. Reetz, M.M. Drewes, K. Harms and W. Reif. In particular, a compound of formula (Fd) in an inert solvent, preferably methylene chloride, is added to a suspension of equimolar amount of $ZnBr_2$ in an inert solvent, preferably methylene chloride, at -30°C to about -10°C, preferably at -20°C. After about 15 to 40 minutes, preferably after about 30 minutes, trimethylsilyl cyanide is added to the $ZnBr_2$ solution. The resulting mixture is stirred at -30°C to about -10°C, preferably at -20°C for about 3 to 5 hours, preferably for about 4.5 hours. The compound of formula (Fe) is then isolated from the reaction mixture by conventional isolation techniques, for example, by extraction with an organic solvent, for example, ethyl acetate. HPLC analysis indicates that the compound of formula (Fe) is formed as two distinct diastereomers, i.e., a (2*S*,3*S*) diastereomer and a (2*R*,3*S*) diastereomer, in a 95:5 ratio, respectively.

The compound of formula (Fe) is then treated with a compound of formula $R^{15}OH$, for example, ethanol or methanol, under acid hydrolysis conditions to form a compound f formula (Ff) (Step 4a). Th preferred conditions for this hydrolysis inv lve the bubbling of hydrogen chloride gas into an anhydr us protic s lvent, for example, a 3:1 mixture of ether and ethanol, at low temperatures, for example, 0°C. Normally, 8 to 10 mL of th 3:1 mixture of

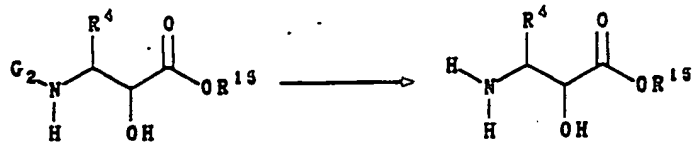
anhydrous ether and absolute ethanol is used for every gram quantity of compound of formula (Fe). A compound of formula (Fe) in a protic solvent, preferably anhydrous ether, is then added to this solution. The resulting mixture is stirred at about 5°C for about 20 to about 28 hours, preferably for about 24 hours. Ice-cold water (0.6 to 0.8 mL per gram of compound of formula (Fe)) is then added to this mixture, which is then stirred for 2 to 3 days, preferably for about 2 days, at about 5°C. The mixture is then neutralized by the addition of base, preferably a mixture of sodium bicarbonate and ethyl acetate. A compound of formula (Ff) and its corresponding amide are then isolated from the neutralized reaction mixture by conventional techniques, for example, by filtration, extraction, and chromatography.

Alternatively, a compound of formula (Ff) may be prepared by the process described by Step 4b of Reaction Scheme 1a. For example, a compound of formula (Fe) is treated with an acid, preferably concentrated hydrochloric acid, at refluxing temperatures for a period of 12 to 20 hours, preferably for about 16 hours. The pH of the resulting mixture is then adjusted with base to about pH 4. The compound of formula (Fg) is then isolated from the reaction mixture by conventional techniques, for example, extraction and chromatography, and then treated with an acidic solution of a compound of formula $R^{15}OH$, preferably a solution of ethanol saturated with hydrogen chloride gas, at room temperature for about 24 hours. The solvent is then removed from the reaction mixture, which is neutralized by base as described above. The compound of formula (Ff) is then isolated from the reaction mixture by conventional methods of extraction.

The amino-protecting groups of the compounds of formula (Ff), i.e., the $G_1$ substituents, are removed by catalytic hydrogenation, for example, by hydrogenating an ethanolic solution of a compound of formula (Ff) over 20% $Pd(OH)_2/C$ at 50 psi $H_2$ over a period of 16 to 24 hours, preferably over a period of 20 hours, to give a compound of formula (F). The preferred conditions are to employ 0.4 gram of the 20% $Pd(OH)_2/C$ catalyst to each gram of compound of formula (Ff) used.

Alternatively, compounds of formula (F) can be prepared from compounds of formula (E) as illustrated below in Reaction Scheme Ib wherein $R^4$ is benzyl; $R^{15}$ is alkyl; and $G_2$ is benzyloxycarbonyl:

Reaction Scheme 1b



(E) (F)

Compounds of formula (E) may be prepared according t the procedures described in R. Herranz et al., *J. Org. Chem.* (1990), V l. 55, pp. 2232-2234; R. Herranz et al., *Synthesis* (1989), pp. 703-706; R. Nishizawa et al., *J. Org.*

*Chem.* (1977), V l. 20, pp. 510-515; F. Matsuda *et al.*, *Chem. Letts.* (1990), pp. 723-724; H. Harada *et al.*, *Chem. Pharm. Bull.* (1989), Vol. 37, No. 9, pp. 2570-2572; K. Iizuka *et al.*, *J. Chem. Soc., Chem. Comm.* (1989), pp. 1678-1680; Y. Ito *et al.*, *Heterocycles* (1990), Vol. 30, pp. 299-302; Y. Kobayashi *et al.*, *Chem. Letts.* (1990), pp. 17C9-1710; K. Iizuka *et al.*, *J. Med. Chem.* (1990), Vol. 33, pp. 2707-2714; D.H. Rich *et al.*, *J. Org. Chem.* (1980), Vol. 45, pp. 2288-2290; R.L. Johnson, *J. Med. Chem.* (1982), Vol. 25, pp. 605-610. Preferably, for the purposes of Reaction Scheme 1b, the compounds of formula (E) are such that the carbon to which the hydroxy is attached is in the "*S*" configuration, and that the carbon to which the $R^4$ substituent is attached is also in the "*S*" configuration.

The amino-protecting group of a compound of formula (E), i.e., the $G_2$ substituent, is removed by catalytic hydrogenation, for example, a solution of a compound of formula (E) in alcohol, preferably methanol or ethanol, is hydrogenated over 10% Pd/C at 50 psi $H_2$ for 6 to 12 hours, preferably, for about 8 hours. The compound of formula (F) is then isolated from the reaction mixture by conventional methods.

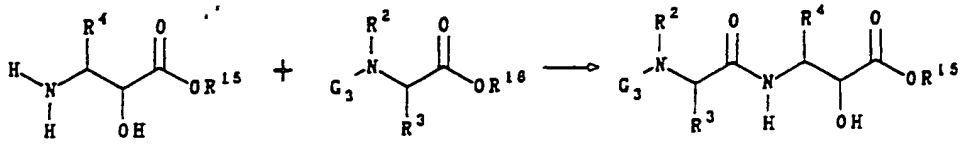
B. Preparation of Compounds of Formula (Ia) and (I)

Compounds of formula (Ia) are compounds of formula (I) wherein $R^1$ is $G_3$, an amino-protecting group selected from the group consisting of t-butoxycarbonyl, 2-(naphth-1-yloxy)ethanoyl and benzyloxycarbonyl; $R^2$, $R^3$, $R^4$ and $R^7$ are as defined above in the Summary of the Invention; $R^5$ is hydrogen and $R^6$ is hydroxy.

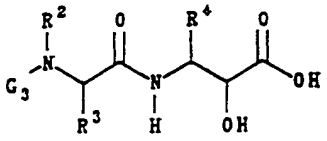
Compounds of formula (Ib) are compounds of formula (I) wherein $R^1$, $R^2$, $R^3$, $R^4$ and $R^7$ are as defined above in the Summary of the Invention; and $R^5$ is hydrogen and $R^6$ is hydroxy.

Compounds of formulae (Ia) and (Ib) are prepared as shown in the following Reaction Scheme 2 where $R^{15}$ is alkyl and $R^{16}$ is hydrogen or *p*-nitrophenyl:

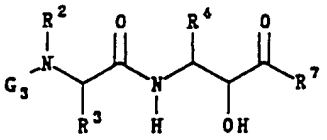
Reaction Scheme 2

1. 

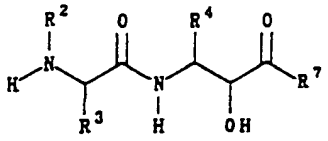
(F) (G) (H)

2. (H) ⟶ 

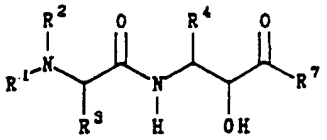
(J)

3. (J) $\xrightarrow{H\text{-}R^7\ (K)}$ 

(Ia)

4. (Ia) ⟶ 

(L)

5. (L) $\xrightarrow{R^1\text{-}OH\ (M)}$ 

(Ib)

Compounds of formula ( ) used in Step 1 of Reaction Scheme 2 are commercially available, for example, benzyloxycarbonyl-L-asparagine *p*-nitrophenyl ester, t-butoxycarbonyl-L-asparagine *p*-nitrophenyl ester, benzyloxycarbonyl L-valine. Other compounds of formula (G), such as

benzyloxycarbonyl-*N'*,*N'*-diethyl-L-asparagine, may be prepared by methods known in the art or by the method illustrated in Preparation 9 below.

Compounds of formula (K) used in Step 3 of Reaction Scheme 2 are prepared according to standard procedures in the peptide literature, e.g., M. Bodansky, A. Bodansky, *The Practice of Peptide Synthesis*, Springer-Verlag, 1984. For example, *t*-butoxycarbonyl-L-proline reacts with *t*-butylamine under standard peptide coupling conditions such as isobutylchloroformate, *N*-methylmorpholine or EDCI/HOBT in an inert solvent such as EDCI to give *t*-butoxycarbonyl-*N'*-*t*-butyl-L-prolinamide. The *t*-butoxycarbonyl group can be removed by treating this compound with HCl gas in dry methylene chloride for a period of 1 to 3 hours, preferably for 1 hour. Removal of the solvent yields *N'*-*t*-butyl-L-prolinamide hydrochloride which can be neutralized with base such as triethylamine in methylene chloride to give the free amine, *N'*-*t*-butyl-L-prolinamide, i.e., a compound of formula (K).

Alternatively, when a benzyloxycarbonyl derivative is used, for example, benzyloxycarbonyl-*N'*-*t*-butyl-L-(4*R*)-hydroxyprolinamide (prepared under similar conditions as described above), the benzyloxycarbonyl group is removed by catalytic hydrogenation. For example, a solution of benzyloxycarbonyl-*N'*-*t*-butyl-L-(4*R*)-hydroxyprolinamide in absolute ethanol is hydrogenated at 50 psi $H_2$ over 10% Pd/C to give the free amine, *N'*-*t*-butyl-L-(4*R*)-hydroxyprolinamide, i.e., a compound of formula (K).

In a similar manner other compounds of formula (K) can be prepared, e.g., octahydroindole-2-*N'*-*t*-butylcarboxamide, octahydroisoindole-3-*N'*-*t*-butylcarboxamide, or *N'*-*t*-butyl-L-(4*S*)-hydroxyprolinamide. Furthermore, the synthesis of individual stereoisomers of an octahydroindoline amino acid was reported in *Tetrahedron Letters*, Vol. 31, No. 34, pp. 4889-4892 and in *Drug Design and Discovery* (1992), Vol. 9, pp. 11-28; and the synthesis of an individual stereoisomer of an azobicyclo[3.3.0]octane amino acid was reported in *Heterocycles* (1989), Vol. 28, p. 957. These examples are for illustrative purposes only and shall not be viewed as limitations on the scope of the invention described herein.

Compounds of formula (M) used in Step 5 of Reaction Scheme 2 are commercially available, for example, 1-naphthoxyacetic acid, 2-naphthoxyacetic acid, quinoline-2-carboxylic acid, for example, from Aldrich Co., or may be prepared by methods known to those of ordinary skill in the art. For example, 6-bromo-2-naphthoxyacetic acid is prepared from ethyl bromoacetate, potassium carbonate and 6-bromo-2-naphthol in DMF, followed by base hydrolysis.

In general, a compound of formula (Ia) is prepared by treating a compound of formula (G), preferably, a compound of formula (G) where $R^{16}$ is *p*-nitrophenyl, in an aprotic solvent, for example, tetrahydrofuran, for a period of up to four days, preferably for three days, at room temperature to form a compound of formula (H) (Step 1 of Reaction Scheme 2).

Alternatively, compounds of formula (H) may be prepared by other peptide couplings, for example, a compound of formula (G) where $R^{16}$ is hydrogen can be treated with 1.1 molar equivalents of HOBt and, preferably, about 2.0 to about

2.5 molar equivalents of EDCI in an aprotic solvent, preferably DMF, under an inert atmosphere, such as argon or nitrogen, at 0°C to about 5°C, for about 30 to about 60 minutes, preferably for about 45 minutes, to afford the activated ester. A molar equivalent amount of a compound of formula (F) in an aprotic solvent, for example, DMF, methylene chloride, or a combination of DMF and methylene chloride is then added to the activated ester in an aprotic solvent, for example, dimethylformamide. The resulting reaction mixture is then stirred at room temperature for about 12 to about 16 hours to afford a compound of formula (H).

A compound of formula (H) can then be hydrolyzed under base conditions, preferably with 1N sodium hydroxide in water/dioxane at 0°C for about 30 to 60 minutes, to give the free acid, i.e., a compound of formula (J) (Step 2 of Reaction Scheme 2).

A compound of formula (J) and a compound of formula (K) are then coupled under similar conditions as described above for the alternate preparation of compounds of formula (H), for example, with EDCI and HOBt in DMF, to afford a compound of formula (Ia) (Step 3 of Reaction Scheme 2).

Alternatively, other peptide couplings may be used to prepare compounds of formula (Ia). For example, the compound of formula (J) can be reacted with about 1 to 1.1 molar equivalent of *N*-methylmorpholine and about 1 to 1.1 molar equivalent of isobutylchloroformate at -10°C to -15°C in an inert solvent, for example, tetrahydrofuran (THF) or DMF, or a combination of both, to afford a mixed anhydride. Subsequent reaction of this mixed anhydride with a compound of formula (K) for 12 hours affords a compound of formula (Ia), which can be isolated from the reaction mixture by conventional isolation techniques standard in the art of peptide chemistry, for example, extraction, column chromatography, and/or HPLC.

The amino-protecting group of a compound of formula (Ia), i.e., the $G_3$ substituent, can be removed when $G_3$ is benzyloxycarbonyl by catalytic hydrogenation, for example, by reacting the compound with 10% Pd/C in absolute ethanol with 50 psi hydrogen, to afford a compound of formula (L) (Step 4 of Reaction Scheme 2).

Compounds of formula (L) are then coupled with compounds of formula (M) under similar conditions as described above for the preparation of compounds of formula (Ia), for example, with EDCI and HOBt in DMF, to afford compounds of formula (Ib) (Step 5 of Reaction Scheme 2).

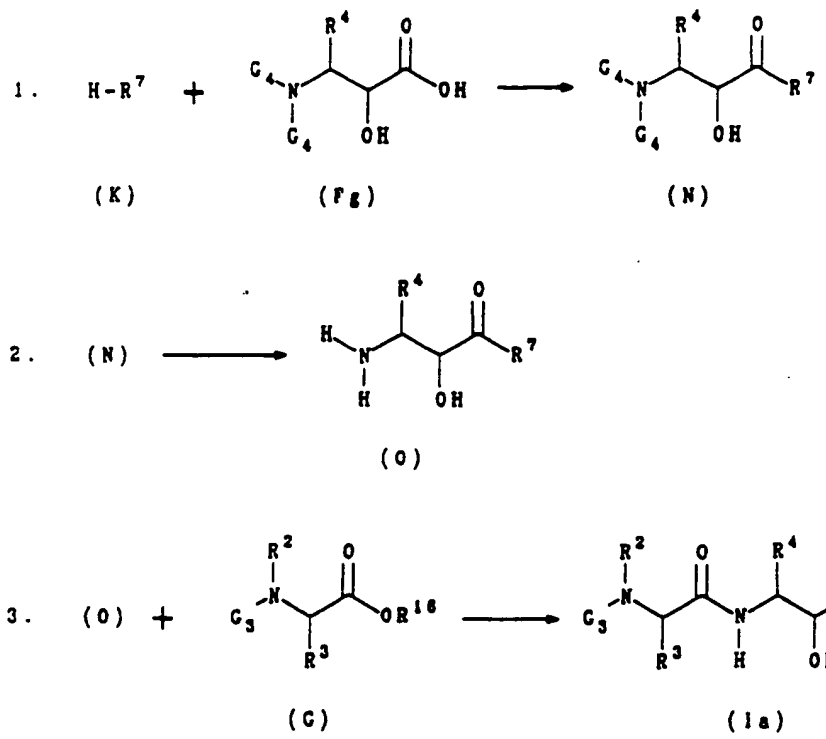
Compounds of formulae (Ia) and (Ib) can further be oxidized by an oxidizing agent, for example, pyridinium dichromate in DMF/$CH_2Cl_2$, or by the methods described in, for example, J.G. Moffat, et al., *J. Am. Chem. Soc.*, Vol. 87, pp. 5661-5669 and 5670-5678, to form compounds of formula (I) wherein $R^5$ and $R^6$ together form oxo.

C. Alternate Method of Preparation of Compounds of Formula (Ia)

Compounds of formula (Ia) are alternately prepared as shown in the following Reaction Scheme 3 where $R^2$, $R^3$, $R^4$ and $R^7$ are as defined above in the Summary of the Invention; $R^{16}$ is hydrogen or *p*-nitrophenyl; each $G_3$ is the same

amino-protecting group selected from the group consisting of t-butoxycarbonyl, 2-(naphth-1-yloxy)ethanoyl and benzyloxycarbonyl; and each $G_4$ is benzyl or one $G_4$ is benzyloxycarbonyl and the other $G_4$ is hydrogen:

**Reaction Scheme 3**




Compounds of formula (K) may be prepared by the methods described earlier in Reaction Scheme 2, or by methods known to those of ordinary skill in the art.

Compounds of formula (Fg) where each $G_4$ is benzyl are prepared as described above in Reaction Scheme 1a. Compounds of formula (Fg) where on $G_4$ is benzyloxycarbonyl and the other $G_4$ is hydrogen are prepared from the corresponding amino acid which has been treated with trimethylsilyl cyanide followed by benzyl chloroformate, as described in Preparation 7E below. Preferably, for the purposes of Reaction Scheme 3, the compounds of formula (Fg) are such that the carbon to which the $R^4$ substituent is attached is in the *S*-configuration, and that the carbon to which the hydroxy group is attached is also in the *S*-configuration.

Compounds of formula (G) are *N*-protected α-amino acids that are commercially available, for example, from Aldrich Co., or may be prepared by methods known to one of ordinary skill in the art.

In general, a compound f formula (Ia) may be prepared by the process described by Reaction Scheme 3 by first reacting a compound of formula (K) with a compound of formula (Fg) wherein b th $G_4$ groups are benzyl under standard peptide coupling conditions known in the art. For example, a solution of a compound of formula (Fg) and an equilmolar amount of H Bt in an

inert solvent, preferably DMF, is cooled to about 0°C. An equilmolar amount f EDCI is then added to the cooled solution and the resulting mixture is stirred at about 0°C for about 40 to about 60 minutes, preferably for about 40 minutes. A compound of formula (K) in an inert solvent, preferably methylene chloride, is then added to this solution, and the resulting mixture is then stirred at room temperature for about 20 to about 26 hours, preferably for about 24 hours. A compound of formula (N) is then isolated from the solution by conventional methods, for example, by extraction and chromatography (Step 1 of Reaction Scheme 3).

Alternately, a compound of formula (Fg) wherein one $G_4$ is hydrogen and the other $G_4$ group is benzyloxycarbonyl is treated with a 1.1 molar equivalent amount of HOBt in an inert solvent, preferably DMF, at 0°C. A 2.0 molar equivalent amount of EDCI is then added to the solution and the resulting mixture is stirred at 0°C for about 30 to 40 minutes, preferably for about 35 minutes. The solution containing the compound of formula (K) as described above is then added to the reaction mixture under similar conditions as described above to form a compound of formula (N) wherein one $G_4$ group is hydrogen and the other $G_4$ group is benzyloxycarbonyl.

The amino-protecting groups of the compounds of formula (N) are then removed by catalytic hydrogenation to form compounds of formula (O). Compounds of formula (N) wherein both $G_4$ groups are benzyl are deprotected by hydrogenating a solution of the compound in alcohol, preferably ethanol over 20% $Pd(OH)_2/C$ at 50 psi hydrogen for a period of about 16 to about 30 hours, preferably for about 24 hours. The preferred conditions require the use of 0.4 to about 0.5 g of 20% $Pd(OH)_2/C$ caralyst per gram of compound of formula (N) (Step 2 of Reaction Scheme 3).

Alternatively, compounds of formula (N) wherein one $G_4$ group is hydrogen and the other $G_4$ group is benzyloxycarbonyl are deprotected by hydrogenating a solution of the compound in alcohol, preferably ethanol, over 10% Pd/C at 50 psi hydrogen for a period of 1 to about 8 hours, preferably for about 2 hours.

A compound of formula (O) is then coupled with a compound of formula (G) under similar conditions as described above for the preparation of compounds of formula (1a) in Reaction Scheme 2, for example, with EDCI, HOBt and DMF, to afford compounds of formula (1a).

In summary, compounds of formulae (Ia) and (Ib), which are compounds of formula (I), are prepared by:

(1) reacting a compound of formula (J) where $G_3$ is an amino-protecting group selected from the group consisting of t-butoxycarbonyl, 2-(naphth-1-yloxy)ethanoyl and benzyloxycarbonyl; $R^2$, $R^3$ and $R^4$ are as defined above in the Summary of the Invention; with a compound of formula (K) where $R^7$ is as defined above in the Summary of the Invention to form a compound f formula (Ia) where $G_3$, $R^2$, $R^3$, $R^4$, and $R^7$ are the same as defined above for the compound of formula (J) and the compound of formula (K); or

(2) treating a compound of formula (L) where $R^2$, $R^3$, $R^4$ and $R^7$ are as defined above in the Summary of the Invention, with a compound of formula (M)

where $R^1$ is as defined above in the Summary of the Invention, to form a compound of formula (Ib) where $R^1$, $R^2$, $R^3$, $R^4$ and $R^7$ are the same as defined above for the compound of formula (L) and the compound of formula (M); or

(3) reacting a compound of formula (O) where $R^4$ and $R^7$ are as defined above for the Summary of the Invention, with a compound of formula (G) where $G_3$ is an amino-protecting group and is selected form the group consisting of t-butoxycarbonyl, 2-(naphth-1-yloxy)ethanoyl and benzyloxycarbonyl; $R^2$ and $R^3$ are as defined above in the Summary of the Invention, and $R^{16}$ is hydrogen or *p*-nitrophenyl; to form a compound of formula (Ia) where $G_3$, $R^2$, $R^3$, $R^4$ and $R^7$ are the same as defined above for the compounds of formulae (O) and (G); or

(4) oxidizing a compound of formulae (Ia) or (Ib) as described above with an oxidizing agent to form a compound of formula (I) where $R^5$ and $R^6$ together form oxo.

In addition, all compounds of formula (I) that exist in free base form may be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic acid. Salts of the compounds of formula (I) can also be converted to the free base form or to another salt.

The following specific preparations and examples are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

**Preparation 1**

Compounds of formula (Fc)

A. A solution of phenylalaninol (10 g, 0.0661 mol) and benzyl bromide (17 mL, 0.146 mol) in 200 mL potassium carbonate solution (30 g) was refluxed for four hours. The solution was cooled and extracted with ethyl acetate, the organic layer was dried over sodium sulphate and evaporated to yield *N,N*-dibenzylphenylalaninol as a crude product. The compound was recrystallized from ether/hexane (yield: 18.5 g solid), m.p. 65-67°C, MS: 331 ($M^+$).

B. A solution of tyrosinol hydrochloride (9.8 g, 0.048 mol) and benzyl bromide (16.5 g, 0.096 mol) in 200 mL potassium carbonate solution (30 g) was refluxed for 8 hours. Benzyl bromide (16.5 g, 0.096 mol) was added and the mixture was refluxed for another 8 hours. The solution was cooled and extracted with ethyl acetate, the organic layer was dried over sodium sulphate and evaporated to the crude product. The material was purified by column chromatography (10% ethyl acetate:hexane to 50% ethyl acetate:hexane) to give 6.05 g of *N,N*-dibenzyl-*O*-benzyltyrosinol, m.p. 112-113°C, and 4.5 g of *N,N*-dibenzyltyrosinol, m.p. 155-156°C.

**Preparation 2**

Compounds of formula (Fd)

A. A solution of dry methylene chloride (100 mL) and oxalyl chloride (5.37 mL, 0.0616 mol) was placed in 500 mL 3-neck flask equipped with a drying tube, a stopper and a septum. DMS (14.21 mL (Aldrich), 0.200 mol) was added slowly at -60°C to -65°C over a period of 2 minutes. The reaction mixture was

stirred for 5 minutes and a solution f *N,N*-dibenzylphenylalaninol (18.5 g, 0.056 mol) in dry $CH_2Cl_2$ (100 mL) was added; stirring was continued for another 5 minutes. Triethylamine (23 ml, 0.165 mol) was added and the reaction mixture warmed up to room temperature. The mixture was poured onto ice-cold water and extracted with $CH_2Cl_2$. The organic layer was evaporated to a very small volume and redissolved in ethyl acetate. The ethyl acetate solution was washed five times with water, dried over sodium sulphate and evaporated to give *N,N*-dibenzylphenylalaninal. This compound was purified by column chromatography (10% ethyl acetate:hexane); yield: 18 g, IR: 1725 $cm^{-1}$.

B. In a similar manner, but replacing *N,N*-dibenzylphenylalaninol with *N,N*-dibenzyl-*O*-benzyltyrosinol, *N,N*-dibenzyl-*O*-benzyltyrosinal was prepared, IR: 1705 $cm^{-1}$; m.p. 75-76°C.

## Preparation 3

## Compounds of Formula (Fe)

A. A solution of *N,N*-dibenzylphenylalaninal (18 g, 0.055 mol) in dry $CH_2Cl_2$ (100 mL) was added to a suspension of $ZnBr_2$ (14.15 g, 0.0618 mL) in dry $CH_2Cl_2$ (100 mL) at -20°C (dry-ice, $CCl_4$) under argon. After 30 minutes, trimethylsilyl cyanide (11.5 mL, 0.084 mol) was added and the mixture was vigorously stirred at -20°C for 4.5 hours. The material was poured onto ice-cold water and extracted. The $CH_2Cl_2$ layer was dried over $MgSO_4$ and evaporated to give an oil. The aqueous phase was further extracted three times with ether, the ether extract was dried over $MgSO_4$ and evaporated to give an oil. This gave a total of 21 g of a crude product, 3-*N,N*-dibenzylamino-2-trimethylsilyloxy-4-phenylbutyronitrile, which could be used without further purification. The product was analyzed by analytical HPLC ($CH_3CN$:$NH_4OAc$ buffer, pH 7; gradient: 100% buffer to 100% $CH_3CN$ over 10 minutes run; flow rate: 3 mL/min.) which indicated that the two diastereomers, (2*S*,3*S*)-3-*N,N*-dibenzylamino-2-trimethylsilyloxy-4-phenylbutyronitrile and (2*R*,3*S*)-3-*N,N*-dibenzylamino-2-trimethylsilyloxy-4-phenylbutyronitrile, were formed in 95:5 ratio, respectively. MS: 413 ($M^+$-Me).

B. In a similar manner, but replacing *N,N*-dibenzylphenylalaninal with *N,N*-dibenzyl-*O*-benzyltyrosinal, 3-*N,N*-dibenzylamino-2-trimethylsilyloxy-4-(4'-benzyloxyphenyl)butyronitrile was prepared, as an oil.

## Preparation 4

## Compounds of Formula (Ff)

A. Hydrogen chloride gas was bubbled into a solution of 150 mL anhydrous ether and 50 mL absolute ethanol for 5 minutes at 0°C. The solution was stirred in an Aldrich cool-stir, which was maintained at 5°C, and a solution of 3-*N,N*-dibenzylamino-2-trimethylsilyloxy-4-phenyl-butyronitrile (21 g, existing as a 95:5 diastereomer mixture, as described above in Preparation 3) in 30 mL ether was added. The mixture was stirred at 5°C for 24 hours. Ice-cold water (25 mL) was added dropwise. The resulting mixture was vigorously stirred at 5°C for another 48 hours. The mixture was neutralized

by adding it slowly to a mixtur of sodium bicarbonate and ethyl acetate in a large beaker. The ins luble inorganic was sucti n-filtered after neutralization and the mixture was extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulphate a-d evaporated to give an oil which was purified by column chromatography (elution gradient: 10% ethyl acetate:hexane to 50% ethyl acetate:hexane). Overlapping fraction of the esters could be further purified by prep-HPLC (silica gel, 15% ethyl acetate:hexane). There was obtained 220 mg of (2*R*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoic acid ethyl ester, 8.2 g of (2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoic acid ethyl ester, as an oil, MS: 402 ($M^+$-H); IR: 3500, 1725 $cm^{-1}$, and 1.1 g of (2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoic acid amide, recrystallized from ethyl acetate:hexane, m.p. 118-119°C; MS: 331 ($M^+$); IR: 3300, 1645, 1655 $cm^{-1}$.

B. In a similar manner, but replacing 3-*N*,*N*-dibenzylamino-2-trimethylsilyloxy-4-phenyl-butyronitrile with 3-*N*,*N*-dibenzylamino-2-trimethylsilyloxy-4-(4'-benzyloxyphenyl)butyronitrile, the following compounds were made:

(2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-(4'-benzyloxyphenyl)butanoic acid ethyl ester, oil, MS: 510 ($M^+$); and

(2*R*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-(4'-benzyloxyphenyl)butanoic acid ethyl ester, oil, MS: 510 ($M^+$).

**Preparation 5**

Compounds of Formula (Ff) (Step 4b)

A. A solution of (2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-trimethylsilyloxy-4-phenylbutyronitrile and (2*R*,3*S*)-3-*N*,*N*-dibenzylamino-2-trimethylsilyloxy-4-phenylbutyronitrile (2 g, 95:5 diastereomeric mixture) in dioxane (15 mL) was mixed with concentrated HCl and refluxed for 16 hours. The material was evaporated to dryness. A small amount of water was added and the pH of the solution was adjusted to pH 4 with $NH_4OH$. The solution was extracted with ethyl acetate, the organic layer was dried over sodium sulphate and evaporated to give an oil. Column chromatography (elution gradient: 50% ethyl acetate:hexane to ethyl acetate to 12% MeOH:$CH_2Cl_2$) gave 450 mg of 3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoic acid, as an oil. The aqueous phas was purified by ion-exchange chromatography to give another 60 mg of the acid as a white solid, m.p. >250°C; MS: 374 ($M^+$ -H).

B. (2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoic acid (780 mg) was added to a saturated solution of hydrogen chloride in absolute ethanol. The mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and the residue was mixed with ethyl acetate and $NaHCO_3$ soluti n. The mixture was extracted, the organic layer was dried over sodium sulphate, and evaporated t give an oil, which was purifi d by c lumn chromatography (18% ethyl acetate:hexan ) to give (2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoic acid ethyl ester as an oil, yield: 800 mg.

Preparation 6

Compounds of Formula (F) (As prepared by Reaction Scheme 1a)

A. $Pd(OH)_2/C$ (1.3 g, Aldrich) was added slowly to a solution of (2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoic acid ethyl ester (2.6 g) in absolute ethanol (200 mL) in a Parr bottle under argon. The solution was hydrogenated at 50 psi $H_2$ for 16 hours. The solution was flushed with argon and the catalyst filtered through Celite. The filtrate was evaporated to give (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid ethyl ester as an oil, yield: 1.31 g, MS: 224 $(M+H)^+$.

B. In a similar manner, the following compound was made: (2*S*,3*S*)-3-amino-2-hydroxy-4-(4'-hydroxyphenyl)butanoic acid ethyl ester, MS: 240 $(MH)^+$.

Preparation 7

Compounds of Formula (E)

A. *N*-Methylpiperidine (8.20 mL, 66.8 mmol) was added to a suspension of *N*-methyl-*O*-methylhydroxyamine hydrochloride (8.14 g, 83.5 mmol) in $CH_2Cl_2$ (50 mL) at 0°C and the resulting mixture was stirred at 0°C for 30 minutes. Meanwhile, *N*-methylpiperidine (8.20 mL, 66.8 mmol) was added to a solution of benzyloxycarbonyl-L-phenylalanine (20 g, 66.8 mmol) in $CH_2Cl_2$ (50 mL) and tetrahydrofuran (50 mL) at 10°C. Methyl chloroformate (5.21 mL, 66.8 mmol) was added dropwise at -10°C to this solution, and the resulting mixture was stirred for 10 minutes. The solution of the *N*-methyl-*O*-methylhydroxyamine in $CH_2Cl_2$ was added and the resulting mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was partitioned between $CH_2Cl_2$ and water. The organic layer was washed with 0.2 N NaOH, brine, dried over $Na_2SO_4$ and evaporated to give crude benzyloxycarbonyl-L-phenylalanyl-*N*-methyl-*O*-methylamide. The product was further purified by column chromatography (30% ethyl Acetate:hexane to 70%) to give 13.5 g of benzyloxycarbonyl-L-phenylalanyl-*N*-methyl-*O*-methylamide as an oil.

B. $LiAlH_4$ (332 mg, 8.73 mmol) was added portionwise to 25 mL of dry tetrahydrofuran at 0°C under argon. A solution of benzyloxycarbonyl-L-phenylalanyl-*N*-methyl-*O*-methylamide (3 g, 8.76 mmol) in dry tetrahydrofuran (50 mL) was added slowly at 0°C over 15 minutes, and the resulting mixture was stirred for 60 minutes at the same temperature. A mixture of ethyl acetate and tetrahydrofuran (50 mL each) was added slowly. After 15 minutes, the mixture was poured slowly into ice-cold 1N HCl (100 mL) and then extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over $Na_2SO_4$ and evaporated to give an oil which was further purified by column chromatography (30% ethyl acetate: hexane) to give benzyloxycarbonyl-L-phenylalaninal as a solid (2.11 g).

C. A solution of $NaHSO_3$ (0.773 g, 7.42 mmol) in water (5 mL) was added slowly to a solution of benzyloxycarbonyl-L-phenylalaninal (2 g) in acetonitrile (5 mL) at 5°C and the mixture was stirred at 5°C overnight. Ethyl acetate (60 mL) and a solution of KCN (0.966 g, 14.84 mmol) in water (10

mL) were added and the resulting mixture were stirred at room temperature for 4 hours. The organic layer was washed with water, dried over $Na_2S_4$ and evaporated to give the cyan hydrin as an oil (2.24 g).

D. A solution of the cyanohydrin (2.24 g) in dioxane (5 mL) and concentrated HCl (15 mL) was refluxed for 16 hours. The solution was cooled, adjusted to pH 7 with 2N NaOH and extracted with ether. The aqueous extract was loaded onto an ion-exchange column (Cation exchange resin AG50W-X8, 100-200 mesh hydrogen form). The material was eluted with water (500 mL), followed by 1N $NH_4OH$. The basic extract was evaporated to about 2 mL and mixed with acetone, the insoluble solid was filtered to give 3-amino-2-hydroxy-4-phenylbutanoic acid (1.45 g).

E. Trimethylsilyl cyanide (3.07 mL, 23 mmol) was added to a suspension of 3-amino-2-hydroxy-4-phenylbutanoic acid (1 g, 5.12 mmol) in $CH_3CN$ (20 mL) and stirred for 20 minutes. The suspension was cooled to 5°C, benzyl chloroformate (0.81 mL, 5.6 mmol) was added slowly and the mixture was stirred at room temperature for 4 hours. The mixture was mixed with ice-cold water and evaporated to remove $CH_3CN$. The residue was extracted between ethyl acetate and water, the organic layer was dried over $Na_2SO_4$ and evaporated to give 3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid as a solid (1.1 g).

F. A mixture of benzyloxycarbonyl-L-phenylalaninal (4.1 g, 14.57 mmol) and tributyltin cyanide (5.53 g, 17.48 mmol) in dry $CH_2Cl_2$ (150 mL) was stirred at -40°C for 30 minutes. The mixture was evaporated to dryness, the crude cyanohydrin was dissolved in a dried and cooled mixture of ether/methanol (3:1) at 0°C, previously saturated with HCl (100 mL). The solution was stirred at 5°C for 24 hours, ice-cold water (15 mL) was added dropwise, and the resulting mixture was stirred at 5° to 10°C for 48 hours. The mixture was concentrated and extracted with $CH_2Cl_2$. The organic layer was washed with water and brine, dried over $Na_2SO_4$ and evaporated to give an oil (4 g). The material was purified by column chromatography (28% ethyl acetate:hexane) to give (2*S*,3*S*)-3-benzyloxy-carbonylamino-2-hydroxy-4-phenylbutanoic acid methyl ester (700 mg, m.p. 121-122°C) and (2*R*,3*S*)-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid methyl ester (2 g, m.p. 94-95°C).

## Preparation 8

### Compounds of Formula (F) (As prepared by Reaction Scheme 1b)

A. A solution of (2*S*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid methyl ester (1 g, 2.91 mmol) in anhydrous methanol was hydrogenated over 10% Pd/C at 50 psi hydrogen for 12 hours. The catalyst was filtered through Celite and the filtrate evaporated to give an oil. The oil was dissolved in ethyl acetate and dried over s dium sulphate. Solvent evaporation gave (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid methyl ester, as an il (610 mg), MS: 208 ($M^+$-H).

B. In a similar manner, but replacing (2*S*,3*S*)-3-benzyloxycarbonyl-

amino-2-hydroxy-4-phenylbutanoic acid methyl ester with the appropriate compound of formula (E), the following compound was made: (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid methyl ester, as an oil.

Preparation 9

Compounds of Formula (G)

A. 1,1'-carbonyldiimidazole (0.689 g, 4.23 mmol) was added to a solution of benzyloxycarbonyl-L-aspartic acid benzyl ester (1.513 g, 4.23 mmol) in dry THF and the resulting solution was stirred at room temperature for 3 hours. Diethylamine (0.466 mL, 98% pure, 4.23 mmol) was added and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue taken up in ethyl acetate. The ethyl acetate solution was washed successively with 1N HCl, 0.5N NaOH, brine and dried over sodium sulphate. The solvent was evaporated *in vacuo* to give benzyloxycarbonyl-L-*N'*,*N'*-diethylasparagine benzyl ester as an oil (1.05 g), IR: 3320-3340, 1715, 1625 $cm^{-1}$; MS: 412 ($M^+$). This oil could be used without further purification.

B. In a similar manner, but replacing diethylamine with ethyl amine, the following compound of formula (G) was prepared: benzyloxycarbonyl-L-*N'*-ethylasparagine benzyl ester, m.p. 127-128°C; MS: 384 ($M^+$).

C. Benzyloxycarbonyl-L-*N'*,*N'*-diethylasparagine benzyl ester (1.05 g) was hydrolyzed in 1N NaOH (8 mL) and dioxane (8 mL) at 0°C for 30 minutes. The solution was acidified with 3N HCl and evaporated to remove dioxane. The aqueous material was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and evaporated to give benzyloxycarbonyl-L-*N'*,*N'*-diethyl-asparagine (650 mg) as an oil, MS: 322 ($M^+$).

D. In a similar manner, but replacing benzyloxycarbonyl-L-*N'*,*N'*-diethylasparagine benzyl ester with benzyloxycarbonyl-L-*N'*-ethylasparagine benzyl ester, the following compound of formula (G) was prepared: benzyloxycarbonyl-L-*N'*-ethylasparagine, m.p. 145-146°C; MS: 294 ($M^+$).

E. *Tert*-butoxycarbonyl-L-aspartic acid β-benzyl ester (2 g, 6.19 mmol) was added to a saturated solution of ammonia gas in absolute ethanol (100 mL). The solution was stirred at room temperature for two days. Solvent evaporation gave an oil which was extracted between ether and water. The aqueous layer was acidified with 3N HCl to pH of 1 and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over sodium sulphate and evaporated to give 1.25 g of t-butoxycarbonyl-L-*N'*-methylasparagine as a white solid, m.p. 164-165°C.

F. Alternatively, *N*-methylmorpholine (2.9 g, 28.7 mmol) was added to a solution of 1-naphthoxyacetic acid (5.06 g, 25.02 mmol) in dry THF (25 ml) at -15°C, followed by the addition of isobutyl choloroformate (3.5 g, 25.62 mmol). After 5 minutes, a solution of L-valine benzyl ester.HOTs salt (9.65 g, 25.43 mmol) in THF (30 ml) and $Et_3N$ (2.9 g, 28.71 mmol) was added. The

mixture was stirred at -15°C for 2 hours and then at room temperature for 18 hours. The material was concentrated under reduced pressure, and extracted with ethyl acetate and water. The organic extract was washed with water, saturated $NH_4Cl$ solution, brine, dried over sodium sulphate, and evaporated to give an oil. This material was purified by column chromatography (25% ethyl acetate:hexane) to give the 2-(naphth-1-yloxy)ethanoyl-L-valine benzyl ester (8.25 g).

G. Proceeding, a solution of 2-(naphth-1-yloxy)ethanoyl-L-valine benzyl ester (4.38 g, 11.8 mmol) from above was hydrogenated over 10% Pd/C in absolute ethanol (100 ml) at 50 psi $H_2$ for 1 hour. A thick precipitate was formed, the suspension was diluted with $CH_2Cl_2$ and suction filtered through Celite. The filtrate was concentrated to give 2-(naphth-1-yloxy)ethanoyl-L-valine as a white solid (3.3 g), m.p. 199-201°C.

**Preparation 10**

Compounds of formula (H)

A. A solution of (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid methyl ester (610 mg, 2.95 mmol) and benzyloxycarbonyl-L-asparagine *p*-nitrophenyl ester (1.13 g, 2.92 mmol) in dry THF was stirred under argon for 2 days. The solvent was removed under reduced pressure and the residue purified by column chromatography (10% MeOH:$CH_2Cl_2$) to give (2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid methyl ester as a white solid (513 mg), m.p. 218-219°C.

B. In a similar manner, but replacing (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid methyl ester with (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid methyl ester, the following compound was made: (2*R*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid methyl ester, m.p. 188-189°C.

C. In a similar manner, but replacing (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid methyl ester with (2*S*,3*S*)-3-amino-2-hydroxy-4-(4'-hydroxy)phenylbutanoic acid methyl ester, the following compound was made: (2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-(4'-hydroxy)-phenylbutanoic acid ethyl ester, m.p. 190-192°C, MS: 488 $(M+H)^+$.

**Preparation 11**

Alternate Preparation of Compounds of formula (H)

A. EDCI (0.65 g, 1.43 mmol) was added to a solution of benzyloxycarbonyl-L-*N'*,*N'*-diethylasparagine (0.46 g, 1.43 mmol) and HOBt (0.193 g, 1.43 mmol) in dry DMF under argon at 0°C. The resulting solution was stirred at 0°C for 20 minut s. A solution of (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutan ic acid methyl ester (0.29 g, 1.43 mmol) in dry DMF was added and the solution was stirred overnight at room temperature. Th solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The rganic layer was washed successively with 1N HCl, 0.5N Na H, and brine s lution. The organic solvent phase was dried over

magnesium sulphate and evaporated to give (2*S*,3*S*)-3-(benzyloxycarbonyl-L-*N'*,*N'*-diethylasparaginyl)amino-2-hydroxy-4-phenylbutanoic acid methyl ester as an oil (297 mg); IR: 3300,1720,1660,1620 $cm^{-1}$.

B. In a similar manner, the following compound of formula (H) was made:

(2*S*,3*S*)-3-(benzyloxycarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoic acid ethyl ester, m.p. 160-162°C;

C. Alternatively, in a similar manner, the following compound of formula (H) wherein $G_3$ is 2-(naphth-1-yloxy)ethanoyl were made:

(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoic acid ethyl ester, m.p. 181-182°C; and

(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-D-valyl)amino-2-hydroxy-4-phenylbutanoic acid ethyl ester, m.p. 171-173°C.

## Preparation 12

## Compounds of formula (J)

A. Sodium hydroxide solution (1N, 5 mL) was added to a solution of (2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoic acid methyl ester (400 mg, 0.875 mmol) in dioxane (5 mL) at 0°C and the mixture was stirred for 30 minutes. A white gummy solid appeared and the suspension was acidified to pH 7 with 3N HCl. The solvent was removed *in vacuo* and the residue was acidified to pH 1 with 3N HCl. The insoluble solid was filtered and washed with ethyl acetate. This gave (2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid as a white solid (150 mg), m.p. 213-214°C. The ethyl acetate wash was separated from the water and dried over sodium sulphate; the solvent was removed *in vacuo* to give another crop of the product (50 mg).

B. In a similar manner, but replacing (2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid methyl ester with (2*R*,3*S*)-3-(benzyloxy-carbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid methyl ester, the following compound of formula (J) was made:

(2*R*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid, m.p. 195-196°C.

C. In a similar manner, but replacing (2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid methyl ester with (2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-(4'-hydroxy)phenylbutanoic acid ethyl ester, the following compound was made:

(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-(4'-hydroxy)-phenylbutanoic acid, m.p. 229-230°C, MS: 460 $(\dot{M}+H)^+$.

D. In a similar manner, the following compound was made:

(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoic acid, m.p. 180-182°C.

**Preparation 13**

**Alternate Preparation f Compounds of formula (J)**

A. Sodium hydroxide solution (1N, 5 mL) was added slowly t a solution of (2*S*,3*S*)-3-(benzyloxycarbonyl-L-*N'*,*N'*-diethylasparaginyl)amino-2-hydroxy-4-phenylbutanoic acid methyl ester (297 mg, 0.578 mmol) in dioxane (5 mL) at 0°C. After 30 minutes, the solution was acidified with 3N HCl and the solvent was evaporated to remove the dioxane. The aqueous material was extracted with ethyl acetate (2 x 100 mL). The combined organic phase was washed successively with brine, dried over sodium sulphate and evaporated to give (2*S*,3*S*)-3-(benzyloxycarbonyl-L-*N'*,*N'*-diethylasparaginyl)amino-2-hydr xy-4-phenylbutanoic acid as a clear oil (200 mg), which could be recrystallized from ether/$CH_2Cl_2$/hexane, m.p. 138-139°C, IR: 3320, 3340, 2500-3200(br), 1720, 1700, 1660 $cm^{-1}$.

B. In a similar manner, the following compound of formula (J) was prepared:
(2*S*,3*S*)-3-(benzyloxycarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoic acid, m.p. 190-192°C.

**Preparation 14**

**Amino-protected compounds of Formula (K) and Compounds of Formula (K)**

A. Finely powdered 2-t-butyloxacarbonyloximinophenylacetonitrile (2.06 g, 8.5 mmol) was added to a stirred solution of L-pipecolic acid (1 g, 7.66 mmol) and triethylamine (1.62 mL, 11.49 mmol) in water (6 mL) and di xane (6 mL). After about one hour the mixture became homogeneous; stirring was continued for two more hours. Water (80 mL) and ethyl acetate (120 mL) wer added, the aqueous layer was separated and re-extracted with ethyl acetate. The aqueous layer was acidified with citric acid, and then extracted with ethyl acetate (3 x 80 mL). The organic phase was washed successively with water, dried over sodium sulphate and evaporated to give *N*-t-butyloxycarbonyl-L-pipecolic acid, 1.29 g, m.p. 122-123°C.

B. Proceeding, EDCI (2 g, 10.2 mmol) was added to a solution of *N*-t-butyloxy-carbonyl-L-pipecolic acid (1.17 g, 5.1 mmol) and HOBt (0.69 g, 5.1 mmol) in dry DMF under argon at 0°C. The resulting solution was stirred at 0°C for 20 minutes. A solution of t-butylamine (0.54 mL, 5.1 mmol) in dry DMF (2 mL) was added and the resulting solution was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was washed successively with 1N HCl, 0.5N NaOH, and brine solution. The organic solvent phas was dried over magnesium sulphate and evaporated to give a crude product as a br wn oil. This oil was purified by column chromatography (40% ethyl acetate:hexan ) to give pure (2*S*)-*N*-t-butyl xycarbonylpiperidine-2-*N'*-t-butyl-carboxamide (1.05 g) m.p. 132-133°C; IR. 3310, 1660 $cm^{-1}$.

C. In a similar manner as above, the following compounds were made:
*N*-t-but xycarbonyl-*N'*-t-butyl-L-prolinamide, m.p. 192-193°C;

*N*-t-butoxycarbonyl-*N'*-t-butyl-D-prolinamide, m.p. 123-124°C;
*N*-t-butoxycarbonyl-*N'*-(1-hydroxy-2-methylpropyl-2-yl)-L-prolinamide, m.p. 192-193°C;
*N*-t-butoxycarbonyl-*N'*-(pyrid-2'-ylmethyl)-L-prolinamide, m.p. 123-124°C;
*N*-t-butoxycarbonyl-*N'*-(2-(pyrid-2'-yl)ethyl)-L-prolinamide, m.p. 124-126°C;
*N*-t-butoxycarbonyl-*N'*-cyclohexyl-L-prolinamide, m.p. 142-143°C;
*N*-t-butoxycarbonyl-*N'*-(2-(morpholin-4-yl)ethyl)-L-prolinamide, m.p. 127-128°C;
*N*-t-butoxycarbonyl-*N'*-t-butyl-L-phenylalaninamide, m.p. 131-133°C;
*N*-t-butoxycarbonyl-*N'*-t-butyl-L-cyclohexylalaninamide, m.p. 164-165°C;
*N*-benzyloxycarbonyl-*N'*-t-butyl-(4*R*)-hydroxy-L-prolinamide, m.p. 124-125°C;
(2*S*,3a*S*,7a*S*)-1-t-butoxycarbonyloctahydroindole-2-*N'*-(1-benzylpiperidin-4-yl), as a white foam;
(2*S*,3a*S*,7a*S*)-1-t-butoxycarbonyloctahydroindole-2-*N'*-*iso*-propylcarboxamide, m.p. 136-137°C;
(4*S*)-3-butoxycarbonylthiazolidine-4-*N'*-t-butylcarboxamide, m.p. 131-133°C; and
*N*-benzyloxycarbonyl-*N'*-t-butyl-(4*S*)-hydroxy-L-prolinamide, m.p. 129-130°C.

D. In a similar manner as above, *N*-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (2.41 g) was converted to *N*-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-*N'*-t-butylcarboxamide. The material was used without further purification. A solution of the amide in absolute ethanol was hydrogenated over 10% Pd/C at 50 psi $H_2$ for 16 hours. The catalyst was filtered through Celite and the filtrate evaporated to give 1,2,3,4-tetrahydroisoquinoline-3-*N'*-t-butylcarboxamide (580 mg). This material was redissolved in absolute ethanol and hydrogenated over 5% Rh/alumina for 3 hours at 60 psi $H_2$. The catalyst was filtered through Celite under suction, and the filtrate evaporated to give (3*RS*,4a*RS*,8a*RS*)-decahydroisoquinoline-3-*N'*-t-butylcarboxamide (415 mg), IR: 3300,1655 $cm^{-1}$.

E. Alternatively, (3*S*,4a*S*,8a*S*)-decahydroisoquinoline-3-*N'*-t-butylcarboxamide can be prepared according to the procedure described in European Published Patent Application 0 432 695 (J.A. Martin and S. Redshaw).

F. Octahydro-1*H*-isoindole-1-carboxylic acid hydrochloride was prepared according to the procedures described in the following references: G. Gignarella, R. Cerri, G. Grella, P. Sanna; *Gazzette Chimica Italiana* (1976), Vol. 106, pp. 65-75; C.J. Blankley, J.S. Kaltenbronn, D.E. DeJohn, A. Werner, L.R. Bennett, G. Bobowski, U. Krolls, D.R. Johnson, W.M. Pearlman, M.L. Hoefle, A.D. Essenburg, D.M. Cohen and H.R. Kaplan, *J. Med. Chem.* (1987), Vol. 30, pp. 992-998. Octahydroindole-(2*S*)-carboxylic acid can be obtained commercially from Kawaken Fine Chemicals Co. Ltd, Japan. Proceeding in a similar manner as described above, octahydro-1H-isoindole-1-carboxylic acid hydrochloride and (2*S*,3a*S*,7a*S*)-octahydroind le-2-carboxylic acid were converted into the following compounds:
1-*N'*-t-butylcarbamoyl-2-t-butoxycarbonyloctahydr -1*H*-isoindole;
IR: 1660-1680, 3320 $cm^{-1}$;

(2*S*,3a*S*,7a*S*)-2-*N'*-t-butylcarbamoyl-1-t-butoxycarbonyloctahydroindole, m.p. 116-117°C; and

(2*S*,3a*S*,7a*S*)-2-*N'*-*iso*-pr pylcarbamoyl-1-t-butoxycarbonyloctahydroindole, m.p. 139-140°C.

G. Alternatively, a mixture of formic acid (42 μL, 1.1 mmol) and triethylamine (0.15 mL, 1.1 mmol) in toluene (5 mL) was added to a solution of triphenylphosphine (289 mg, 1.1 mmol) and (4*R*)-hydroxy-*N'*-t-butyl-L-prolinamide (321 mg, 1 mmol) in toluene (20 mL) and DMF (5 mL) at room temperature. A solution of diethyl azidodicarboxylene (DEAD) (0.10 mL, 1.1 mmol) in toluene (5 mL) was then added and the mixture was stirred for 1 day at room temperature. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic extract was dried over sodium sulphate and evaporated to give an oil which was purified by column chromatography (40% ethyl acetate:hexane) to give (4*S*)-*N*-benzyloxycarbonyl-4-formyl-*N'*-t-butyl-L-prolinamide, 260 mg; IR: 1712, 1690 $cm^{-1}$.

H. Proceeding, a solution of (4*S*)-*N*-benzyloxycarbonyl-4-formyl-*N'*-t-butyl-L-prolinamide (206 mg, 0.591 mmol) in methanol (3 mL) and dioxan (15 mL) was mixed with 1N NaOH (3 mL) and stirred at 0°C for 10 minutes. The solution was neutralized to pH of 7 with 3N HCl and then evaporated to remove all organic solvent. The aqueous material was extracted with ethyl acetate, and the organic layer further washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over sodium sulphate and evaporated to give (4*S*)-hydroxy-*N*-benzyloxycarbonyl-*N'*-t-butyl-L-prolinamide, 157 mg, m.p. 129-130°C.

I. Proceeding, a solution of t-butyl isocyanate (0.09 mL, 0.77 mmol) and (4*S*)-hydroxy-*N*-benzyloxycarbonyl-*N'*-t-butyl-L-prolinamide (200 mg, 0.622 mmol) in toluene was refluxed for 3 days. The solvent was evaporated to dryness and the residue partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate and evaporated to give an oil which was purified by column chromatography (40% ethyl acetate:hexane) to give (4*R*)-(*N''*-t-butyl)carbamoyloxy-*N*-benzyloxycarbonyl-*N'*-t-butyl-L-prolinamide, 100 mg. H-NMR (80 MHz): 1.26 (m,18H,2t-Bu), 2.2-2.4 (m,2H,$CH_2$), 3.6-3.7 (m,2H,$CH_2$), 4.3 (m,1H,CH), 5.16 (s,2H,$CH_2$), 7.33 (s,5H,Ph).

J. Proceeding in a similar manner as described above, (4*S*)-hydroxy-*N*-benzyloxycarbonyl-*N'*-t-butyl-L-prolinamide was converted to (4*R*)-(*N''*-t-butyl)carbamoyloxy-*N*-benzyloxycarbonyl-*N'*-t-butyl-L-prolinamide; H-NMR (80 MHz): 1.30 (2s,18H,2t-Bu), 2.2-2.4 (m,2H,$CH_2$), 3.6-3.7 (m,2H,$CH_2$), 4.3 (m,1H,CH), 5.20(s,2H,$CH_2$), 7.35 (s,5H,Ph).

K. Alternatively, Sodium hydride (542 mg, 50% oil, 11.3 mmol) was added slowly to a solution of (4*R*)-ethoxy-*N*-benzyloxycarb nyl-L-proline (1.5 gm, 5.65 mm l) in dry THF (100 mL). The soluti n was stirred at r om temperature for 45 minutes. Ethyl iodide (1.78 g, 11.3 mmol) was added and the mixture was refluxed f r 3 hours and then stirred at room temperature for 18 hrs. Th s lvent was evaporated to dryness and the residue partitioned between ethyl acetat and water. The aqueous layer was acidified t pH of 1

with 3N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and evaporated to give 1 g. (4*R*)-ethoxy-*N*-benzyloxycarbonyl-L-proline, as an oil. Without further purification, a solution of (4*R*)-ethoxy-*N*-benzyloxycarbonyl-L-proline (500 mg, 1.7 mmol) and HOBt (261 mg, 1.7 mmol) in dry DMF (20 mL) was mixed with EDCI (811 mg, 4.25 mmol) and stirred at 0°C for 60 minutes. *Tert*-butylamine (0.19 mL, 1.7 mmol) was added and the mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue partitioned between ethyl acetate and water. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over sodium sulphate and evaporated to give an oil. The oil was purified by column chromatography (40% ethyl acetate:hexane) to give 244 mg of (4*R*)-ethoxy-*N*-benzyloxycarbonyl-*N'*-*t*-butyl-L-prolinamide; MS: 318 ($M^+$).

L. Proceeding, a solution of (4*R*)-ethoxy-*N*-benzyloxycarbonyl-*N'*-*t*-butyl-L-prolinamide (200 mg) in dry ethanol (50 mL) was hydrogenated over 10% Pd/C at 50 psi $H_2$ for 2 hours. The solution was suction filtered through Celite and the filtrate was evaporated to give an oil which was purified by column chromatography (10% MeOH:$CH_2Cl_2$) to give (4*R*)-ethoxy-*N'*-*t*-butyl-L-prolinamide (70 mg) as an oil; MS: 215 $(M+H)^+$.

M. Alternatively, *N*-methylmorpholine (1.3 g, 12.9 mmol) was added to a solution of *N*-*t*-butoxycarbonyl-L-proline (2.1 g, 9.77 mmol) in dry THF (25 mL) at -15°C, followed by the addition of isobutyl chloroformate (1.34 g, 9.77 mmol). After 5 minutes, a solution of 2-aminopyridine (0.91 g, 9.7 mmol) in THF was added. The mixture was stirred at -15°C for 2 hours and then at room temperature for 18 hours. The material was concentrated under reduced pressure, and then extracted with ethyl acetate and water. The organic extract was washed with water, saturated $NH_4Cl$ solution, brine, dried over sodium sulphate, and evaporated to give an oil. This material was purified by column chromatography (40% ethyl acetate:hexane) to give (2*S*)-*N*-*t*-butoxycarbonyl-*N'*-pyrid-2-yl-L-prolinamide (380 mg).

N. Proceeding, (2*S*)-*N*-*t*-butoxycarbonyl-*N'*-pyrid-2-yl-L-prolinamide (262 mg, 0.9 mmol) was mixed with a solution of $CH_2Cl_2$ (70 mL), presaturated with HCl gas, for 2 hours in an ice bath. The solvent was evaporated to dryness and the residue mixed with ethyl acetate (60 mL) and $Et_3N$ (10 mL). The suspension was filtered and the filtrate evaporated to give (2*S*)-*N'*-pyrid-2-yl-L-prolinamide as an oil (164 mg).

O. Alternatively, a racemic mixture of (1*S*,3*S*,5*S*)-endo-2-azabicyclo[3.3.0]octane-3-carboxylic acid and (1*R*,3*R*,5*R*)-endo-2-azabicyclo[3.3.0]octane-3-carboxylic acid was prepared according to the procedur of V. Teetz, R. Geiger, H. Gaul, *Tetrahedron Letters* (1984), p. 4479. To a solution of the racemic mixture (1.1 gm, 6.3 mmol) in dioxane (3 mL), water (3 mL) and $Et_3N$ (1.3 mL, 9.5 mmol) was added 2-*t*-butoxycarbonyloximino-2-phenylacetonitrile (1.57 g, 6.3 mmol). The mixture was stirred at room temperature for 2 hours, and then extracted with ethyl

acetate. The aqueous extract was acidified with citric acid and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried ver sodium sulphate and evaporated to giv a racemic mixture of (1*S*,3*S*,5*S*)-2-(t-butoxycarbonyl)-endo-2-azabicyclo[3.3.0]octane-3-carboxylic acid and (1*R*,3*R*,5*R*)-2-(t-butoxycarbonyl)-endo-2-azabicyclo[3.3.0]octane-3-carboxylic acid, as an oil (1.26 g), MS: 255 $(MH)^+$.

P. Proceeding, t-butylamine (0.25 ml, 2.3 mmol) was coupled with th racemic mixture formed in Paragraph O above (589 mg, 2.3 mmol) using the EDCl (440 mg, 2.3 mmol) and HOBt (353 mg, 2.3 mmol) procedure cited above in Paragraph B. The product was purified by column chromatography (30% ethyl acetate:hexane to 100% ethyl acetate) to give a racemic mixture of (1*S*,3*S*,5*S*)-2-(t-butoxycarbonyl)-endo-2-azabicyclo[3.3.0]octane-3-t-butylcarboxamide and (1*R*,3*R*,5*R*)-2-(t-butoxycarbonyl)-endo-2-azabicyclo[3.3.0]octane-3-t-butylcarboxamide (530 mg), m.p. 129-130°C.

Q. Alternatively, LDA (1.5 M THF solution from Aldrich, 13.9 mL, 20.8 mmol) was added to a solution of (1*S*,3a*S*,7a*R*)-2-t-butoxycarbonyloctahydroisoindole-1-*N*'-t-butylcarboxamide and (1*R*,3a*R*,7a*S*)-2-t-butoxycarbonyloctahydroisoindole-1-*N*'-t-butylcarboxamide (1 g, 5.4 mmol) in dry THF at 0°C and the mixture was stirred for 1 hour. The reaction was quenched with acetic acid and the mixture partitioned between ethyl acetate and 1.5 N HCl. The organic phase was dried over sodium sulphate and evaporated to give an oil. This oil was recrystallized from 20% ethyl acetate:hexane to give a solid. Without purification, this solid was added to 20% HCl solution and refluxed for 24 hours. The material was concentrated to give an oil which was pumped overnight. The oil was mixed with THF (20 mL) and $Et_3N$ (3 mL). Di-t-butyl pyrocarbonate (2.4 g, 11 mmol) was added to the mixture and the resulting mixture was stirred for 8 hours. The material was evaporated to dryness and partitioned between 1N HCl and ethyl acetate. The organic phase was dried over sodium sulphate and evaporated to give an oil. This oil was mixed with EDCl (1.5 g, 8.1 mmol), t-butylamine (0.85 mL, 8.1 mmol), 4-dimethylaminopyridine (100 mg, 0.81 mmol) in $CH_2Cl_2$ at 0°C. After stirring at room temperature for 16 hours, the mixture was washed with water and 1N HCl. The organic phase was dried over sodium sulphate and evaporated to give a diastereomeric mixture of 2-t-butoxycarbonyloctahydroisoindole-1-*N*'-t-butylcarboxamide. The mixture was separated on HPLC (25% ethyl acetate: hexane, silica gel) to give a less polar component, which was the recovered starting material (600 mg). The polar component was the racemic mixture of (1*R*,3a*S*,7a*R*)-octahydroisoindole-1-*N*'-t-butylcarboxamide and (1*S*,3a*R*,7a*S*)-octahydroisoindole-1-*N*'-t-butylcarboxamide (150 mg). Without purification, this racemic mixture (150 mg) was treated with 15% $CF_3COOH$ in $CH_2Cl_2$ for 16 hours. Th s lvent was evaporated to give an oil which was mixed with $Et_3N$ (0.3 mL) and $CH_2Cl_2$ (10 mL). After 30 minutes, the material was evaporated to dryness and purified by c lumn chromatography (10% MeOH:$CH_2Cl_2$) t give 104 mg of a white f am, which was (1*R*,3a*S*,7a*R*)-octahydroisoindole-1-*N*'-t-butylcarboxamide and (1*S*,3a*R*,7a*S*)-octahydr is indole-1-*N*'-t-butylcarboxamide.

R. Alternatively, t-butylchloroacetamidate (1.73 g, 15.2 mmol) was added to a solution of *N*-benzyloxycarbonyl-(L)-pyroglutamic acid (2 g, 7.6 mmol) in $CH_2Cl_2$ (25 mL) and cyclohexane (25 mL), followed by $BF_3Et_2O$ (0.2 mL). The mixture was stirred overnight and the insoluble material filtered. The filtrate was washed with $NaHCO_3$ solution, dried over sodium sulphate and evaporated to give an oil. This oil was purified by column chromatography (50% ethyl acetate:hexane) to give *N*-benzyloxycarbonyl-L-pyroglutamic acid t-butyl ester (1.26 g). Ethylmagnesium bromide solution (1.9 mL, 1M solution in THF, Aldrich) was added to a solution of *N*-benzyloxycarbonyl-L-pyroglutamic acid t-butyl ester (1.23 g, 3.7 mmol) in dry THF (20 mL) at -40°C. The mixture was stirred at that temperature for 2 hours at which time the reaction was quenched with dropwise addition of 3N HCl. The solution was extracted with ethyl acetate. The organic layer was dried over sodium sulphate and evaporated to give an oil. Column chromatography (silica gel, 20% ethyl acetate:hexane) gave (2*S*)-2-benzyloxycarbonylamino-5-oxoheptanoic acid t-butyl ester, as an oil (356 mg), IR:3350, 1730, 1710, 1690 $cm^{-1}$.

S. Proceeding, a solution of tert-butyl 2(*S*)-carbobenzyloxyamino-5-oxo-heptanoiate (300 mg) in absolute ethanol was hydrogenated over 10% Pd/C at 50 psi. $H_2$ for 16 hours. The catalyst was suction filtered through Celite, the filtrate evaporated to give an oil. The oil was chromatographed (50% ethyl acetate:hexane to ethyl acetate) to give 5(*S*)-ethyl-L-proline t-butyl ester (120 mg), as an oil.

T. Alternatively, diethyl 3-phenylpyrrolidine-2,2-dicarboxylate can be prepared according to the procedure of Cox D.A., *et al.*, *J. Chem. Soc.* (1964), p. 5024. To a solution of diethyl 3-phenylpyrrolidine-2,2-dicarboxylate was dissolved in 4N NaOH and stirred at room temperature for 16 hours, 10 mL of concentrated HCl was added and the mixture was refluxed for 6 hours. The solution was cooled and KOH pellet was added to bring the pH to 12. The solution was chilled to 0°C and a solution of benzyloxycarbonyl chloride in 15 mL dioxane was added. The solution was stirred for 20 hours at room temperature and then extracted with ether. The aqueous layer was acidified to pH 2 with HCl and extracted four times with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and evaporated to give 1-benzyloxycarbonyl-3-phenylproline as a solid, which was recrystallized from ethyl acetate:hexane (1.2 g), m.p. 165-166°C, MS:324 $(M-H)^-$.

U. Proceeding, a solution of 1-benzyloxycarbonyl-3-phenylproline in dry DMF (1.01 g, 3.07 mmol) was mixed with EDCI (1.46 g, 7.6 mmol) and HOBt (470 mg, 3.07 mmol) at 0°C. After 1 hour, a solution of t-butylamine (0.40 mL, 0.24 mmol) in dry DMF (4 mL) was added. After stirring for 16 hours, the solution was evaporated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic extract was washed with saturated sodium bicarbonate solution, brine, dried over sodium sulphate and evaporated to give an oil. The material was purified by column chromatography (30% ethyl acetate:hexane) to give two diastereomers. The less polar diastereomer was assigned the racemic mixture of *cis*-1-benzyloxy-

carbonyl-3-phenyl-*N'*-t-butyl-D,L-prolinamide (160 mg, oil, m.p. 143-144°C) and the more polar diastereomer was assigned the racemic mixture of *trans*-1-benzyl xycarbonyl-3-phenyl-*N'*-t-butyl-D,L-prolinamide (480 mg, solid), m.p. 144-145°C.

V. Proceeding, a solution of *trans*-1-benzyloxycarbonyl-3-phenyl-*N'*-t-butyl-D,L-prolinamide (440 mg, 1.15 mmol) in absolute ethanol was hydrogenated over 10% Pd/C at 50 psi $H_2$ for 2hours. The catalyst was filtered through Celite and the residue was evaporated to give a solid. The material was purified by column chromatography to give 244 mg of *trans*-3-phenyl-*N'*-t-butyl-D,L-prolinamide as a yellow solid, m.p. 110-111°C.

W. Proceeding in a similar manner, *cis*-3-phenyl-*N'*-t-butyl-D,L-prolinamide was obtained as an oil.

X. Proceeding in a similar manner as described above in Paragraphs T, U and V, diastereomers of 3-ethyl-*N'*-t-butylprolinamide were prepared.

**Preparation 15**

**Compounds of formula (L)**

A. A solution of 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl-amino)-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide (191 mg, 0.414 mmol) in absolute ethanol was hydrogenated at 50 to 60 psi $H_2$ over 10% Pd/C for 6 hours. The catalyst was filtered through Celite, and the filtrate evaporated to give 1-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-phenyl-butanoyl]-*N'*-t-butyl-L-prolinamide as a foamy solid (138 mg, recrystallized from $CH_2Cl_2$/ether, m.p. 92-93°C). MS: 462.2 ($M^+$), 171.

B. In a similar manner, but replacing 1-[(2*S*,3*S*)-3-(benzyloxy-carbonyl-L-asparaginylamino)-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide with the appropriate compound of formula (Ia), the following compounds of formula (L) were made:

1-[(2*S*,3*S*)-3-L-*N'*,*N'*-diethylasparaginylamino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, 133 mg; as an oil;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N'*-t-butylcarboxamide, 160 mg, m.p. 104-105°C;

1-[(2*S*,3*S*)-3-L-valylamino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, oil; and

(2*S*)-1-[(2*S*,3*S*,)-3-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]piperidine-2-*N'*-t-butylcarboxamide.

C. In a similar manner, the following compounds were made:

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-((2*S*)-ethylglycyl)amino-2-hydroxy-4-phenyl-butanoyl] ctahydroind le-2-*N'*-t-butylcarboxamide, as a white s lid;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-L-valylamino-2-hydr xy-4-phenylbutan yl]-octahydr indol -2-*N'*-t-butylcarboxamide, m.p. 148-149°C;

1:1 mixture f (1*S*,3a*R*,7a*S*)-1-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]octahydroisoindol -1-*N'*-t-butylcarboxamide and (1*R*,3a*S*,7a*R*)-1-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-

4-phenylbutanoyl]octahydroisoindole-1-*N'*-t-butylcarboxamide;
1:1 mixture of (1*S*,3a*S*,7a*R*)-1-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N'*-t-butylcarboxamide and (1*R*,3a*R*,7a*S*)-1-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N'*-t-butylcarboxamide;
1:1 mixture of (1*S*,3*S*,5*S*)-1-[(2*S*,3*S*)-3-(L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-azabicyclo[3.3.0]octane-3-*N'*-t-butylcarboxamide and (1*R*,3*R*,5*R*)-1-[(2*S*,3*S*)-3-(L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-azabicyclo[3.3.0]octane-3-*N'*-t-butylcarboxamide; and
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-(4'-hydroxy)-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide, m.p. 85-86°C.

**Preparation 16**

Compounds of Formula (M)

A. Ethyl bromoacetate (1.68 mL, 15.15 mmol) was added to a suspension of 6-bromo-2-napthol (3.5 g, 97% pure, 15.21 mmol) and potassium carbonate (2.7 g, 19.56 mmol) in dry DMF (40 mL), followed by tetra-*N*-butylammonium iodide (100 mg). The mixture was stirred for 16 hours and filtered. The filtrate was evaporated to give an oil which was then extracted with ethyl acetate and water. The organic layer was dried over magnesium sulphate, evaporated to give a solid which was recrystallized from $CH_2Cl_2$/hexane. This gave ethyl 6'-bromo-2'-naphthoxyacetate as a white solid, 3.72 g; m.p. 86-87°C; MS: 308 ($M^+$).

B. In a similar manner, the following compounds were made:
ethyl 1'-bromo-2'-naphthoxyacetate, m.p. 73-74°C;
ethyl 3-hydroxymethyl-phenoxy acetate;
ethyl quinolin-8'-yloxyacetate, oil; and
ethyl quinolin-4'-yloxyacetate, m.p. 159-160°C.

C. Proceeding, NaOH (1N, 20 mL) was added to a solution of ethyl 6'-bromo-2'-naphthoxyacetate (3.3 g) in DME (30 mL), and the solution was stirred for 60 minutes. The mixture was acidified to pH of 1 with 3N HCl, and the organic solvent was then removed under reduced pressure. The insoluble solid was extracted with acetone/water (4:1) and the insoluble material filtered. The filtrate was evaporated to give 6'-bromo-2'-naphthoxyacetic acid as a solid (2.8 g); m.p. 230-232°C.

D. In a similar manner, the following compounds were made:
1'-bromo-2'-naphthoxyacetic acid, m.p. 163-164°C;
quinolin-8'-yloxyacetic acid, MS: 203 ($M^+$); and
quinolin-4'-yloxyacetic acid, m.p. 179-180°C.

E. Alternatively, ethyl 2-pyridoxyacetate was prepared according to the procedures f J. Maas, *et al.*, *Recueil des travaux Chimiques des pays-bas* (1955), Vol. 74, pp. 175-178. NaOH solution (150 mg NaOH, 6.26 mmol in 7 mL water) was added to a solution of ethyl 2-pyridoxyacetate (0.5 g, 2.76 mmol) in dioxane. The material was left stirring at 0°C for 18 hours and room temperature for 30 minutes. The s lution was acidifed with concentrated HCl

to pH 5 and then concentrated under reduced pressure. The residue was azeotroped with $CH_3CN$ several times to remove water. A yellow residue was formed which was mixed with $CH_3CN$ (4 ml) and filtered. This gave 220 mg of 2-pyridoxyacetic acid as a yellow solid. M.p. 111-113°C.

F. Alternatively, 4-pyridoxyacetic acid was prepared according to the procedures of H.J. Den, *et al.*, *Chem. Pharm. Bull.*, Vol. 23, No. 11, pp. 3008-3010.

G. Alternatively, mesyl chloride (0.44 ml, 5.68 mmol) was added to a solution of ethyl 3-hydroxymethylphenoxy acetate (1.1 g, 5.23 mmol) and $Et_3N$ (0.9 mL, 6.5 mmol) in $CH_2Cl_2$ (25 ml) at 0°C. After 2 hours, a solution of imidazole (0.44 g, 6.5 mmol) and $Et_3N$ (0.9 mL, 6.5 mmol) in DMF (3 mL) was added and the mixture was stirred overnight at room temperature. The material was concentrated and then partitioned between ethyl acetate and water. The organic phase was dried over sodium sulphate and evaporated to give crude ethyl 3-(imidazolylmethyl)phenoxyacetate. This material was mixed with 1N NaOH (30 mL) and MeOH (30 mL) and stirred at room temperature for 4 hours. MeOH was removed under reduced pressure and the aqueous material was extracted with ether (50 mL). The aqueous layer was acidified to pH 2 with 6N HCl and again washed with ether (50 mL). This acidic solution was applied onto Bi Rad AG50W-X8 100-200 Mesh cation exchange resin (2 x 12 cm) and eluted with water. The product was eluted with 20% pyridine/water (300 ml). Solvent evaporation gave 3-(imidazolylmethyl)phenoxyacetic acid as a semi-solid which was dried to constant weight (0.5 g). M.p. 69-70°C.

H. In a similar manner, the following compounds were made:
3-(morpholin-4-ylmethyl)phenoxyacetic acid, gum; and
3-([4-methylpiperazin-1-yl]methyl)phenoxyacetic acid, m.p. 188-189°C (decomp.).

**Preparation 17**

**Compounds of Formula (N)**

A. *N*-t-butyloxycarbonyl-*N'*-t-butyl-L-prolinamide (2.23 g, 8.25 mol) was added to a saturated solution of HCl gas in $CH_2Cl_2$ (100 mL) and the resulting solution was stirred at room temperature for 1 hour. The solvent was removed *in vacuo*; the residue pumped under high vacuum for 30 minutes. This material was redissolved in $CH_2Cl_2$ (30 mL) and neutralized with triethylamine (1.15 mL, 8.25 mmol).

B. A solution of (2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoic acid (3.1 g, 8.25 mmol) and HOBt (1.26 g, 8.25 mmol) in dry DMF (20 mL) was cooled to 0°C. EDCI (3.15 g, 8.25 mmol) was added and the solution was stirred at 0°C for 50 min. The solution from paragraph A above was added and the resulting mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacu* and the residue extracted with ethyl acetate and water. The organic layer was washed successively with 1N HCl, brine and dried over sodium sulphate. Solvent evaporation gave a solid which was purified by column chromatography (40% ethyl acetate:hexane). The

material was recrystallized from ether:hexane to give 2.1 g of (2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoyl-*N'*-t-butyl-L-prolinamide as a white solid, m.p. 130-131°C.

C. Alternatively, compounds of formula (N) wherein one $G_1$ group is hydrogen were prepared as follows:

*N*-t-butyloxycarbonyl-*N'*-t-butyl-L-prolinamide (820 mg, 3.03 mmol) was added to a saturated solution of HCl gas in $CH_2Cl_2$ (50 mL) and the resulting solution was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue pumped under high vacuum for 30 minutes. This material was redissolved in $CH_2Cl_2$ and neutralized with triethylamine (0.1 mL). A solution of (2*RS*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid (1 g, 3.04 mmol) and HOBt (580 mg, 3.28 mmol) in dry DMF was cooled to 0°C. EDCI (1.45 g, 7.59 mmol) was added and the solution was stirred at 0°C for 35 minutes. The solution containing *N*-t-butyloxycarbonyl-*N'*-t-butyl-L-prolinamide was added and the mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and the residue extracted with ethyl acetate and water. The organic layer was washed with 1N HCl, brine and dried over sodium sulphate. Solvent evaporation gave a solid which was purified by column chromatography (60% ethyl acetate:hexane) to give 1-[(2*R*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide (less polar isomer, 438 mg) and 1-[(2*S*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide (more polar isomer, 320 mg); MS: 482.2$(M+H)^+$.

## Preparation 18

### Compounds of Formula (O)

A. $Pd(OH)_2/C$ (200 mg, Aldrich) was added slowly to a solution of the 1-(2*S*,3*S*)-3-*N*,*N*-dibenzylamino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide (800 mg) in absolute ethanol (100 mL) in a Parr bottle under argon. The solution was hydrogenated at 50 psi $H_2$ for 16 hrs. The solution was flushed with argon and the catalyst filtered through Celite. The filtrate was evaporated to give an oil which was further purified by column chromatography (elution gradient: ethyl acetate to 10% MeOH:$CH_2Cl_2$ to 20% MeOH:$CH_2Cl_2$) to yield 281 mg of 1-[(2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 144-145°C.

B. Alternatively, certain compounds of formula (O) may be prepared as follows: (2*S*,3a*S*,7a*S*)-octahydroindole-2-*N'*-t-butylcarboxamide (0.83 g, 3.7 mmol) was coupled to (2*S*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid (1.15 g, 3.49 mmol) using the procedure shown in Example 4D below. The product was recrystallized from $CH_3CN$ to give (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide (1.44 g), m.p. 91-93°C. A solution of (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-benzyl xycarbonylamino-2-hydroxy-4-phenylbutan yl]octahydroindole-2-*N'*-t-butylcarboxamide (1.31 g, 2.45 mmol) in absolute ethanol (100 mL) was hydrogenated over 10% Pd/C (178 mg) at 50 psi $H_2$ for 5 h urs. The catalyst

was removed by sucti n filtration through Celite. Solvent evaporation gave an oil which was purified by column chromatography (1% $Et_3N$:10% MeOH:$CH_2Cl_2$) to give 850 mg of (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N'*-t-butylcarboxamide, m.p. 75-77°C.

**Example 1**

Compounds of formula (Ia) (As prepared by Reaction Scheme 2)

A. *Tert*-butyloxycarbonyl-*N'*-t-butyl-L-prolinamide (135 mg, 0.496 mmol) was added to a saturated solution of HCl gas in $CH_2Cl_2$ and the resulting solution was stirred at room temperature for 1 hour. The solvent was removed *in vacuo*; the residue pumped under high vacuum for 30 minutes. The residue was re-dissolved in $CH_2Cl_2$ and neutralized with $Et_3N$ (0.1 mL) t afford a solution of *N'*-t-butyl-prolinamide. A solution of (2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid (220 mg, 0.496 mmol) and HOBt (67 mg, 0.496 mmol) in dry DMF was cooled to 0°C. EDCI (237 mg, 1.24 mmol) was added and the solution was stirred at 0°C for 20 minutes. The solution of *N'*-t-butyl-L-prolinamide prepared above was added and the mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and the residue extracted with ethyl acetate and water. The organic layer was washed successively with 1N HCl, brine and dried over sodium sulphate. Solvent evaporation gave a solid which was purified by column chromatography (10% MeOH:$CH_2Cl_2$) and thick layer plate chromatography (10% MeOH:$CH_2Cl_2$) to give 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide as a solid (191 mg; m.p. 116-118°C), MS: 596.3($M^+$).

B. Proceeding in a similar manner, but replacing (2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid with the appropriate compound of formula (J), the following compounds of formula (Ia) were made:

1-[(2*R*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenyl-butanoyl]-*N'*-t-butyl-L-prolinamide; m.p. 192-193°C; MS: 595(M+), 495,496,398; and

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-*N'*,*N'*-diethylasparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 90-94°C, MS: 651 ($M^+$).

C. In a similar manner, but replacing t-butyloxycarbonyl-*N'*-t-butyl-L-prolinamide with the appropriate precursor of a compound of formula (K), e.g., (2*S*,3a*S*,7a*S*)-*N*-(t-butyloxycarbonyl)octahydroindole-2-*N'*-t-butylcarboxamide, the following compounds of formula (Ia) were made:

(2*S*)-1-[(2*S*,3*S*,)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]piperidine-2-*N'*-t-butylcarb xamide, m.p. 87-89°C;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide, m.p. 108-110°C;

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-(1-hydroxy-2-methylprop-2-yl)-L-prolinamide, m.p. 138-140°C;

1-[(2*S*,3*S*,)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-(1,2,3,4-tetrahydroisoquinoline)-3-carboxylic acid t-butyl ester, m.p. 103-104°C;

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-D-prolinamide, m.p. 138-140°C;

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-(2-pyrid-2'-ylethyl)-L-prolinamide, m.p. 151-153°C;

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-(pyrid-2'-ylmethyl)-L-prolinamide, m.p. 108-110°C;

(1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N'*-t-butylcarboxamide, m.p. 97-100°C;

(1*R*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N'*-t-butylcarboxamide, as an oil;

(4*R*)-1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-4-hydroxy-*N'*-t-butyl-L-prolinamide, m.p. 122-124°C;

(4*S*)-1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-4-hydroxy-*N'*-t-butyl-L-prolinamide, m.p. 123-124°C;

(4*R*)-1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-4-t-butylcarbamoyloxy-*N'*-t-butyl-L-prolinamide, m.p. 114-116°C;

(4*S*)-1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-4-t-butylcarbamoyloxy-*N'*-t-butyl-L-prolinamide, m.p. 127-128°C;

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-cyclohexyl-L-prolinamide, m.p. 120-122°C;

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-(2-(morpholin-4-yl)ethyl)-L-prolinamide, m.p. 126-128°C;

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 204-205°C; and

(3*S*,4a*S*,8a*S*)-2-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]decahydroisoquinoline-3-*N'*-t-butylcarboxamide, m.p. 113-115°C.

D. In a similar manner, the following compounds were made:

(2*S*)-1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-*N'*-(pyrid-2-yl)-L-prolinamid , m.p. 140-142°C;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl] ctahydroindole-2-*N'*-(1-benzylpiperidin-4-yl)carboxamide, m.p. 110-112°C;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-

2-hydroxy-4-phenylbutanoyl] ctahydroindol -2-*N'-iso*-propylcarboxamid , m.p. 108-110°C;

(4*S*)-3-[(2*S*,3*S*)-3-(2-naphth-1-yloxy)ethanoyl-L-valylamino-2-hydroxy-4-phenylbutanoyl]thiazolidine-*N'*-t-butylcarboxamide, m.p. 154-155°C;

(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide, m.p. 224-226°C;

1:1 mixture of (1*S*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N'*-t-butylcarboxamide and (1*R*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroisoindole-1-*N'*-t-butylcarboxamide;

1:1 mixture of (1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N'*-t-butylcarboxamide and (1*R*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroisoindole-1-*N'*-t-butylcarboxamide, MS: 650.4 $(MH)^+$;

(1*S*,3*S*,5*S*)-*N*-[(2*S*,3*S*)-3-benzyloxycarbonyl-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]-*endo*-2-azabicyclo[3.3.0]octane-3-*N'*-t-butylcarboxamide, m.p. 108-110°C;

(1*R*,3*R*,5*R*)-*N*-[(2*S*,3*S*)-3-benzyloxycarbonyl-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]-*endo*-2-azabicyclo[3.3.0]octane-3-*N'*-t-butylcarboxamide, m.p. 104-105°C;

(3*S*,4a*R*,8a*R*)-2-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]decahydroisoquinoline-3-*N'*-t-butylcarboxamide, m.p. 114-117°C;

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-*trans*-3-phenyl-L-prolinamide, m.p. 208-210°C (more polar diastereomer) and 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-*trans*-3-phenyl-L-prolinamide, m.p. 144-146°C (less polar diastereomer);

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-*cis*-3-phenyl-L-prolinamide, m.p. 204-206°C (more polar diastereomer) and 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-*cis*-3-phenyl-L-prolinamide, m.p. 112-113°C (less polar diastereomer);

1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-*trans*-3-ethyl-L-prolinamide, m.p. 191-192°C (more polar diastereomer) and 1-[(2*S*,3*S*)-3-(benzyl xycarb nyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-*trans*-3-ethyl-L-prolinamide,

m.p. 108-112°C (less polar diastereomer);
1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-*cis*-3-ethyl-L-prolinamide, m.p. 203-204°C (more polar diastereomer) and 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-*cis*-3-ethyl-L-prolinamide, m.p. 104-106°C (less polar diastereomer);
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-(4'-hydroxy)phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide, m.p. 146-148°C; and
1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-5-ethyl-L-proline t-butyl ester, m.p. 106-107°C.

E. EDCI (161 mg, 0.845 mmol) was added to a solution of HOBt (45 mg, 0.338 mmol) and (2*S*,3*S*)-3-benzyloxycarbonyl-L-asparaginylamino-2-hydroxy-4-phenylbutanoic acid (150 mg, 0.338 mmol) in dry DMF at 0°C and the resulting mixture was stirred at the same temperature for 20 min. A solution of (3*RS*,4a*RS*,8a*RS*)-decahydroisoquinoline-3-*N'*-t-butylcarboxamide (71 mg, 0.338 mmol) in dry DMF was added. After stirring at room temperature for 16 hours, the solvent was removed *in vacuo*; the residue was taken up in ethyl acetate. The organic material was washed successively with water, 1N HCl and brine, dried over sodium sulphate and evaporated to give an oil which was chromatographed over 10% MeOH:$CH_2Cl_2$ to give (3*RS*,4a*RS*,8a*RS*)-2-[(2*S*,3*S*)-3-benzyloxycarbonyl-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]decahydroisoquinoline-3-*N'*-t-butylcarboxamide (110 mg), m.p. 127-130°C.

## Example 2

### Compounds of Formula (Ia) (As prepared by Reaction Scheme 3)

A. A solution of benzyloxycarbonyl-L-*N'*-ethyl-asparagine (114 mg, 0.389 mmol) and HOBt (60 mg, 0.389 mmol) in dry DMF (15 mL) was cooled to 0°C. EDCI (186 mg, 0.973 mmol) was added and the solution was stirred at 0°C for 55 min. A solution of 1-[(2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide (135 mg, 0.389 mmol) in dry $CH_2Cl_2$ (10 mL) was added and the mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and the residue extracted with ethyl acetate and water. The organic layer was washed with 1N HCl, brine and dried over sodium sulphate. Solvent evaporation gave a solid which was purified by column chromatography (10% MeOH:$CH_2Cl_2$) and thick layer plate chromatography (10% MeOH:$CH_2Cl_2$) to give 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-*N'*-ethylasparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide (120 mg), m.p. 100-102°C; MS: 624.5$(M+H)^+$.

B. In a similar manner, but replacing benzyloxycarbonyl-L-*N'*-ethylasparagine with the appropriate compound of formula (G), the following compound of formula (Ia) was made:
1-[(2*S*,3*S*)-3-(t-butoxycarbonyl-L-*N'*-methylasparaginyl)amino-2-hydroxy-

4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide; m.p. 118-120°C;

C. In a similar manner, the f llowing compound was made: (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-((2*S*)-ethyl)glycyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide, m.p. 219-220°C.

**Example 3**

Compounds of formula (Ib)

A. A solution of quinaldic acid (36 mg, 0.207 mmol) and HOBt (27 mg, 0.2 mmol) in dry DMF (15 mL) was cooled to 0°C under argon. EDCI (93 mg, 0.486 mmol) was added and the solution was stirred at 0°C for 20 minutes. A solution of 1-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide (89 mg, 0.193 mmol) in dry $CH_2Cl_2$ was added and the resulting solution was stirred at room temperature for 24 hours in the dark. The solvent was removed in vacuo and the residue taken up with ethyl acetate. The organic layer was washed successively with water, sodium bicarbonate solution and brine, dried over sodium sulphate and evaporated to give an oil. The material was purified by column chromatography (80% acetone:hexane to acetone) and thick layer plate chromatography (10% MeOH:$CH_2Cl_2$) to give 1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide (45 mg), m.p. 129-130°C; recrystallized from $CH_2Cl_2$:hexane, MS: 617.3($M^+$), 600.1.

B. In a similar manner, but replacing 1-[(2*S*,3*S*)-3-L-asparaginyl-amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide with other compounds of formula (L), the following compounds of formula (Ib) were made: 1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-*N'*-ethylasparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 120-122°C; (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide, m.p. 139-141°C; and (3*S*,4a*S*,8a*S*)-2-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]decahydroisoquinoline-3-*N'*-t-butylcarboxamide, m.p. 128-130°C.

C. In a similar manner, but replacing 1-[(2*S*,3*S*)-3-L-asparaginyl-amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide with 1-[(2*S*,3*S*)-3-L-valylamino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, the following compound of formula (Ib) was made: 1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-valyl)amino-2-hydroxy-'-phenylbutan yl]-*N'*-t-butyl-L-prolinamide; m.p. 123-125°C.

D. In a similar manner, but replacing quinaldic acid with the appropriate compound f formula (M) and 1-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide with the appropriate compound f f rmula (L), the following compounds f formula (Ib) were made: 1-[(2*S*,3*S*)-3-(2-(6-methoxynaphth-2-yl)ethanoyl-L-asparaginyl)amino-2-hydroxy-

4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 113-115°C;
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amin -2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide, m.p. 128-130°C;
1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 118-119°C;
1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-*N'*-methylasparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 113-115°C;
(2*S*)-1-[(2*S*,3*S*,)-3-(4-bromobenzoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-piperidine-2-*N'*-t-butylcarboxamide, m.p. 122-124°C;
(4*R*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-4-hydroxy-*N'*-t-butyl-L-prolinamide, m.p. 133-135°C;
1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]-*N'*-(1-hydroxy-2-methylprop-2-yl)-L-prolinamide, m.p. 125-127°C;
(4*R*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-4-ethoxy-*N'*-t-butyl-L-prolinamide, m.p. 114-115°C;
1-[(2*S*,3*S*)-3-(2-(6-bromonaphth-2-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 114-115°C;
1-[(2*S*,3*S*)-3-(2-(6-bromonaphth-2-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 135-137°C;
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(6-bromonaphth-2-yloxy)ethanoyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide, m.p. 122-124°C;
1-[(2*S*,3*S*)-3-(2-(1-bromonaphth-2-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 180-181°C;
1-[(2*S*,3*S*)-3-(2-(naphth-2-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 122-123°C;
1-[(2*S*,3*S*)-3-(2-(naphth-2-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 203-204°C;
1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, m.p. 176-178°C;
(1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N'*-t-butylcarboxamide, m.p. 132-134°C; and
(1*R*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl] ctahydroisoind le-1-*N'*-t-butylcarboxamide, m.p. 145-146°C.

E. In a similar manner, the following compounds were made:
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(benzoxazol-2-yl)-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide,

m.p. 159-161°C;
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethan yl-((2*S*)-ethyl)glycyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide, m.p. 117-119°C;
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide, m.p. 103-104°C;
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide, m.p. 130-132°C;
(1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N*'-t-butylcarboxamide, m.p. 141-144°C;
(1*R*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N*'-t-butylcarboxamide, m.p. 144-146°C;
(1*S*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N*'-t-butylcarboxamide, m.p. 125-128°C;
(1*R*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N*'-t-butylcarboxamide, m.p. 123-125°C;
(1*S*,3*S*,5*S*)-*N*-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-azabicyclo[3.3.0]octane-3-*N*'-t-butylcarboxamide, m.p. 109-110°C;
(1*R*,3*R*,5*R*)-*N*-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-azabicyclo[3.3.0]octane-3-*N*'-t-butylcarboxamide, m.p. 125-128°C;
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-phenoxyethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide, m.p. 116-118°C;
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-(4'-hydroxy)phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide, m.p. 210-212°C (decomp.);
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(pyrid-2-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-(4'-hydroxy)phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide, m.p. 148-150°C;
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(3-(morpholino-4-ylmethyl)phenoxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamid , m.p. 108-110°C;
(2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(benzimidaz l-5-yl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroind le-2-*N*'-t-butylcarboxamide, m.p. 108-110°C;

F. A s lution of (3*RS*,4a*RS*,8a*RS*)-2-[(2*S*,3*S*)-3-benzyloxycarbonyl-L-

asparaginylamino-2-hydroxy-4-phenylbutanoyl]decahydroisoquinoline-3-*N'*-t-butylcarboxamide (110 mg, 0.183 mmol) in absolute ethanol was hydrogenated over 10% Pd/C for 6 hours. The catalyst was filtered through Celite under suction, the filtrate was evaporated to give (3*RS*,4a*RS*,8a*RS*)-2-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]decahydroisoquinoline-3-*N'*-t-butylcarboxamide as an oil. Without any further purification, EDCI (48 mg, 41 mmol) was added to a solution of quinaldic acid (24.5 mg, 0.163 mmol) and HOBt (22 mg, 0.163 mmol) in dry DMF at 0°C. After 20 min., a DMF solution of (3*RS*,4a*RS*,8a*RS*)-2-[(2*S*,3*S*)-3-L-asparaginylamino-2-hydroxy-4-phenylbutanoyl]-decahydroisoquinoline-3-*N'*-t-butylcarboxamide was added and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, the residue was taken up in ethyl acetate. The organic mixture was washed successively with 1N HCl, brine, and dried over sodium sulphate. Solvent evaporation gave a product as a solid which was further purified by column chromatography (10% MeOH: $CH_2Cl_2$) to give (3*RS*,4a*RS*,8a*RS*)-2-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginylamino)-2-hydroxy-4-phenylbutanoyl]-decahydroisoquinoline-3-*N'*-t-butylcarboxamide as a white solid, I.R. (KBr): 3340, 1660-1680 $cm^{-1}$.

Example 4

(Compounds of Formula (Ib) wherein $R^1$ is optionally substituted substituted carbamoyl)

A. A solution of 2-aminomethylpyridine (5 g, 46 mmol) in $CH_2Cl_2$ (5 mL) was added to a solution of di-t-butyldicarbonate (10.2 g, 97%, 45.33 mmol) in $CH_2Cl_2$ (80 mL) at 0°C. The reaction mixture was stirred at 0°C for 2 hours, and then warmed up to room temperature overnight. The mixture was extracted with water (2 X 50 mL), dried over sodium sulphate and evaporated to give a yellowish oil (9.1 g). A portion of this material (8.1 g, 38.9 mmol) was dissolved in THF at 0°C. NaH (2.1 g, 52.5 mmol) was added and the mixture was stirred for 15 minutes. Methyl iodide (6.8 g, 47.9 mmol) was added. After stirring for 90 minutes, the reaction was quenched with ice and evaporated to give an oil. The residue was extracted between ether and water, dried over sodium sulphate and evaporated to yield *N*-(t-butoxycarbonyl)-*N*-methyl-*N*-(pyrid-2-ylmethyl)amine, as an oil (6.5 g).

B. Proceeding, *N*-(t-Butoxycarbonyl)-*N*-methyl-*N*-(pyrid-2-ylmethyl)amine (2 g, 9.0 mmol) was added to a saturated solution of HCl gas in dry $CH_2Cl_2$. After 45 minutes, the solution was diluted with $CH_2Cl_2$ (100 mL) and basified to pH 10 by the slow addition of triethylamine. The solution was extracted with water, dried over sodium sulphate and evaporated to give (*N*-methyl-*N*-(pyridin-2-ylmethyl)amine a white s lid (1.06 g). Diphosgene (4 g, 20.2 mmol) was added t dry ethyl acetate (15 mL) at room temperature. A solution f valine methyl ester (3.96 g, 23.6 mmol) was added dropwise. An exothermic reaction took place and the mixture was stirred for 3 hours. Solvent evaporation gave a solid which was pumped to constant weight. This material was chlorocarbonyl-valine methyl ester. Without further

purification, this material (0.99 g) was mixed with a solution of *N*-methyl-*N*-(pyrid-2-ylmethyl)amine (0.6 g) in ethyl acetate (12 mL). After 18 hours at room temperature the filtrate was diluted with ethyl acetate and extracted with saturated sodium bicarbonate solution. The organic extract was washed with brine, dried over sodium sulphate, and evaporated to give an oily residue. This material was chromatographed on silica gel (75% ethyl acetate:hexane) to give *N*-methyl-*N*-(pyrid-2-ylmethyl)carbamoyl-valine methyl ester (0.38 g).

C. Proceeding, NaOH solution (0.5 mL, conc.: 100 mg solid NaOH/mL water, 1.25 mmol) was added to a solution of *N*-methyl-*N*-(pyrid-2-ylmethyl)carbamoyl-valine methyl ester (0.308 g, 1.1 mmol) in dioxane (8 mL) and water (4 mL) at 0°C. After 2 hours, the mixture was stirred at room temperature for 1 hour and neutralized to pH 7 with the addition of two drops of conc. HCl. The material was evaporated to dryness to give *N*-methyl-*N*-(pyrid-2-ylmethyl)carbamoyl-valine sodium salt as a foam (0.33 g).

D. Proceeding, a solution of *N*-methyl-*N*-(pyrid-2-ylmethyl)carbamoyl-valine sodium salt in dry DMF (65 mg, 0.26 mmol) was mixed with EDCl (190 mg, 1 mmol) and HOBt (51 mg, 0.33 mmol) at 0°C. After 1 hour, a solution of (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoyl]octahydroindol -2-*N'*-t-butylcarboxamide (102 mg, 0.24 mmol) in dry DMF (4 mL) was added. After stirring for 16 hours, the solution was evaporated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and water. Th organic extract was washed with saturated sodium bicarbonate solution, brine, dried over sodium sulphate and evaporated to given an oil. The material was purified by column chromatography (5% MeOH:ethyl acetate) to give (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(*N*"-methyl-*N*"-(pyrid-2-ylmethyl)carbamoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide (45 mg), m.p. 109-112°C.

## Example 5

(Alternative Preparation of Compounds of formula (Ia))

A. A solution of 4-t-butoxycarbonylamino-1-benzylpiperidine (3.12 g, 10.7 mmol) in absolute ethanol was hydrogenated over 10% Pd()H)$_2$/C at 50 psi $H_2$ for 3 hrs. This catalyst was removed by suction filtration through Celite. Solvent evaporation gave 4-t-butoxycarbonylamino-piperidine as a white solid (2.1 g), m.p. 159-161°C.

B. Proceeding, 4-t-butoxycarbonylaminopiperidine (1.45 g, 7.25 mmol) was added to a suspension of chlorocarbonyl-valine methyl ester (from Example 4B above, 0.73 g, 3.78 mmol) in ethyl acetate (30 mL). The material was stirred for 20 hours, at room temperature. The insoluble white solid was filtered. Th filtrate was extracted with ethyl acetate and saturated sodium bicarbonate. The organic extract was washed with brine, dried over sodium sulphate and evaporated to give an oil. The material was chromatographed n silica gel (2% MeOH:ethyl acetate) t give (4-(t-butoxycarbonylamino)piperid-1-yl)carbonyl-valine methyl ester as an oil (0.39 g). Part of this material (200 mg) was mixed with dioxane (8 mL) and water (4 mL) at 0°C. NaOH solution

(0.5 mL, conc.: 53 mg NaOH/ml water) was added. The mixture was stirred at 0°C for 2 hours and room temperature for 10 hours. The solution was neutralized to pH 7 with 6N HCl and evaporated to dryness. The solid residue was azeotroped with acetonitrile and pumped to constant weight (188 mg). This material was crude (4-(*t*-butoxycarbonylamino)piperid-1-yl)carbonyl-valine sodium salt, m.p. 110-113°C.

C. Proceeding, (4-(*t*-butoxycarbonylamino)piperid-1-yl)carbonyl-valine sodium salt (154 mg) was coupled to (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-*t*-butylcarboxamide (136 mg, 1.31 mmol) in the same manner as described in Example 4D above to give (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-((4-(*t*-butoxycarbonylamino)piperid-1-yl)carbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-*t*-butylcarboxamide. The product was isolated by column chromatography (75% ethyl acetate:hexane to 100% ethyl acetate), to yield 46 mg, m.p. 149-151°C.

D. Proceeding, (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-((4-(*t*-butoxycarbonyl-amino)piperid-1-yl)carbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octa-hydroindole-2-*N'*-*t*-butylcarboxamide (44 mg, 0.06 mmol) from above was added to a solution of $CH_2Cl_2$ (20 mL) presaturated with HCl gas. The mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure. Ether was added and the insoluble solid was filtered to give (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-((4-aminopiperid-1-yl)carbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-*t*-butylcarboxamide hydrochloride (24 mg), m.p. 210-212°C.

**Example 6**

Oxidation of Compounds of Formulae (Ia) and (Ib)

A. Pyridinium dichromate (360 mg, 0.98 mmol) was added to a solution of 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-*t*-butyl-L-prolinamide (100 mg, 0.173 mmol) in $CH_2Cl_2$ (10 mL) and DMF (2 mL). The solution was stirred at room temperature for 6 hours. The material was poured onto ice-cold water and extracted with $CH_2CL_2$. The organic extract was washed with brine, dried over sodium sulphate, and evaporated to give an oil. The material was purified by column chromatography (10% MeOH:$CH_2CL_2$) and then reverse phase HPLC ($CH_3CN$:50 mM $NH_4OAc$ buffer) to give [(3*S*)-(benzyloxycarbonyl-L-asparaginyl)amino-2-oxo-4-phenylbutanoyl]-*N'*-*t*-butyl-L-prolinamide as a solid (10 mg), m.p. 85-87°C; MS: 594$(M+H)^+$.

B. Alternatively, EDCI (198 mg, 0.1 mmol) was added to a mixture of toluene (4 mL) and DMSO (1 mL). After 15 minutes, 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-*t*-butyl-L-prolinamide (100 mg, 0.173 mmol) and $CF_3COOH$ (0.1 mL) was added. The mixtur was stirred at room temperature f r 24 h urs, and then diluted with ethyl acetate (50 mL). The soluti n was washed five times with water (10 mL each time), dried ver sodium sulphate and evaporated to give an oil. The material was purified by reverse phase HPLC ($CH_3CN$:50 mM $NH_4OAc$ buffer) to give [(3*S*)-(benzyloxycarbonyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]-*N'*-

t-butyl-L-pr linamide as a solid (20 mg), m.p. 85-87°C, MS: 594(M+H)$^+$.

C. In a similar manner, but replacing 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydr xy-4-phenylbutan yl]-*N'*-t-butyl-L-prolinamide with [(2*S*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, a compound of formula (N), the following compound was made:
[(3*S*)-3-benzyloxycarbonylamino-2-oxo-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide, as a foam.

**Example 7**

**Reequilibration of Enantiomers**

Lithium diisopropylamide (0.53 mL, 0.81 mmol, 1.5 M solution in THF) was added to a solution of (2*S*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid methyl ester (110 mg, 0.323 mmol) in dry THF under argon at -78°C and the resulting solution was stirred for 10 minutes. Chlorotrimethylsilane (0.1 ml, 0.64 mmol) was added at -78°C. The mixture was stirred at the same temperature for 40 min., lithium diisopropylamide (0.53 mL, 0.81 mmol, 1.5 M solution in THF) was again added and the mixture was stirred at -78°C for another 45 minutes. The mixture was poured onto ice cold citric acid and extracted with ethyl acetate. The organic phase was washed with 3N HCl and brine, dried over sodium sulphate and evaporated to give an oil. The oil was loaded onto a silica gel column and left for 2 hours before elution with 30% ethyl acetate:hexane to give the two stereoisomers, (2*S*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid methyl ester and (2*R*,3*S*)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid methyl ester. H-NMR indicated the two stereoisomers were formed in about 1:1 ratio (80 mg).

**Example 8**

**Preparation of an Acid Addition Salt of a Compound of Formula (I)**

HCl gas is bubbled into a solution of 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-(2-(morpholin-4-yl)ethyl)-L-prolinamide (100 mg, 0.153 mmol) in methylene chloride (15 mL) for 5 minutes. The solution is stirred at room temperature for 10 minutes and evaporated to dryness. This gives 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-(2-(morpholin-4-yl)ethyl)-L-prolinamide hydrochloride as the product.

**Example 9**

**Preparation of the Free Base from the Salt of a Compound of Formula (I)**

A solution f 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydr xy-4-phenylbutanoyl]-*N'*-(2-(morpholin-4-yl)ethyl)-L-prolinamide hydrochloride (100 mg, 145 mmol) in dry $CH_2Cl_2$ (20 mL) is mixed with triethylamine (0.021 mL, 145 mmol) and stirred at room temperature for 30

minutes. The solution is extracted with water, the organic layer is dried over sodium sulphate and evaporated to give 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-(2-(morpholin-4-yl)ethyl)-L-prolinamide.

**EXAMPLE 10**

This example illustrates the preparation of representative pharmaceutical compositions for oral administration containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, e.g., (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-*t*-butylcarboxamide:

A.

| Ingredients | % wt./wt. |
|---|---|
| Compound of formula (I) | 20.0% |
| Lactose | 79.5% |
| Magnesium stearate | 0.5% |

The above ingredients are mixed and dispensed into hard-shell gelatin capsules containing 100 mg each, one capsule would approximate a total daily dosage.

B.

| Ingredients | % wt./wt. |
|---|---|
| Compound of formula (I) | 20.0% |
| Magnesium stearate | 0.9% |
| Starch | 8.6% |
| Lactose | 79.6% |
| PVP (polyvinylpyrrolidine) | 0.9% |

The above ingredients with the exception of the magnesium stearate are combined and granulated using water as a granulating liquid. The formulation is then dried, mixed with the magnesium stearate and formed into tablets with an appropriate tableting machine.

C.

| Ingredients | |
|---|---|
| Compound of formula (I) | 0.1 g |
| Propylene glycol | 20.0 g |
| Polyethylene glycol 400 | 20.0 g |
| Polysorbate 80 | 1.0 g |
| Water | q.s. 100 mL |

The compound of formula (I) is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of water is then added with stirring to provide 100 mL of the solution which is filtered and bottled.

D.

| Ingredients | % wt./wt. |
|---|---|
| Compound of formula (I) | 20.0% |
| Peanut Oil | 78.0% |
| Span 60 | 2.0% |

The above ingredients are melted, mixed and filled into soft elastic capsules.

**EXAMPLE 11**

This example illustrates the preparation of a representative pharmaceutical formulation for parenteral administration containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, e.g., (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide:

| Ingredients | |
|---|---|
| Compound of formula (I) | 0.02 g |
| Propylene glycol | 20.0 g |
| Polyethylene glycol 400 | 20.0 g |
| Polysorbate 80 | 1.0 g |
| 0.9% Saline solution | q.s. 100 mL |

The compound of formula (I) is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 mL of the I.V. solution which is filtered through a 0.2 $\mu$ membrane filter and packaged under sterile conditions.

**EXAMPLE 12**

This example illustrates the preparation of a representative pharmaceutical composition in suppository form containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, e.g., (1*S*,3*S*,5*S*)-*N*-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-azabicyclo[3.3.0]octane-3-*N*'-t-butylcarboxamide:

| Ingredients | % wt./wt. |
|---|---|
| Compound of formula (I) | 1.0% |
| Polyethylene glycol 1000 | 74.5% |
| Polyethylene glycol 4000 | 24.5% |

The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

**EXAMPLE 13**

This example illustrates the preparation of a representative pharmaceutical formulation for insufflation containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, e.g., (1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N*'-t-butylcarboxamide:

| Ingredients | % wt./wt. |
|---|---|
| Micronized compound of formula (I) | 1.0% |
| Micronized lactose | 99.0% |

The ingredients are milled, mixed, and packaged in an insufflator equipped with a d sing pump.

**EXAMPLE 14**

This example illustrates the preparation of a representative

pharmaceutical formulation in nebulized form containing a compound of formula (I), r a pharmaceutically acceptable salt thereof, e.g., (1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroisoindole-1-*N'*-t-butylcarboxamide:

| Ingredients | % wt./wt. |
|---|---|
| Compound of formula (I) | 0.005% |
| Water | 89.995% |
| Ethanol | 10.000% |

The compound of formula (I) is dissolved in ethanol and blended with water. The formulation is then packaged in a nebulizer equipped with a dosing pump.

**EXAMPLE 15**

This example illustrates the preparation of a representative pharmaceutical formulation in aerosol form containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, e.g., 1-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide:

| Ingredients | % wt./wt. |
|---|---|
| Compound of formula (I) | 0.10% |
| Propellant 11/12 | 98.90% |
| Oleic acid | 1.00% |

The compound of formula (I) is dispersed in oleic acid and the propellants. The resulting mixture is then poured into an aerosol container fitted with a metering valve.

**Example 16**

(*In vitro* assay for inhibition of HIV protease activity)

HIV protease, as encoded in the BRU strain of HIV-1, was obtained from microbially expressed fusion protein, after refolding, autoprocessing and purification, and used to evaluate the potency of compounds of formula (I). The HIV protease-mediated hydrolysis of the peptidyl substrate, *Val-Ser-Gln-Asn-*(β-naphthyl)*Ala-Pro-Ile-Val*, was monitored by modification of the method described in Heimbach, J.C., Garsky, V.M., Michelson, S.R., Dixon, R.A.F., Sigal, I.S. and Darke, P.L., *Biochem. Biophys. Res. Commun.* (1989), Vol. 164, pp. 955-960. Stock solutions of compounds of formula (I) were prepared in dimethylsulfoxide.

Reactions were initiated by addition of 25 μL of 120 pM HIV protease in 50 mM sodium acetate at pH 5.5 containing 10% glycerol, 1 mM dithiothreitol and 1 mg/mL bovine serum albumin to 75 μL of 13.3 μM substrate in 50 mM sodium acetate, pH 5.5 c ntaining 1.33 M sodium chloride, 10% glycerol and 2.66% dimethylsulfoxide, with or without a compound of formula (I). The reaction mixtures were quenched after 30 minutes at 30°C by addition of 100 μL of 12% acetic acid containing 100 μM CBZ-tyr sine, an internal standard to facilitate quantitation of products by HPLC (Perkin-Elmer RP-C18 reverse phase; gradient

eluti n with 0.1% aqueous phosphoric acid/acetonitril mixtures, (80:20) to (50:50) over 5.5 minutes at 2.5 mL/min. Product peaks were detected with a Hewlett-Packard HP 1046A fluorescence detect r, λ(excitation) = 228 nm and λ(emission) = 336 nM. The $IC_{50}$ values were calculated by fitting of data to the equation.

$$V = V_{max}/(1 + [I]/IC_{50})$$

wherein V is the observed rate of the reaction, $V_{max}$ is the uninhibited reaction rate, [I] is the concentration of the compound of formula (I) and $IC_{50}$ is the concentration of the compound of formula (I) required to reduce protease activity by fifty percent.

Compounds of formula (I), when tested by this assay, demonstrated the ability to inhibit HIV protease activity as shown in the following table.

TABLE 1

| No. | Compound | $IC_{50}$ nM |
|---|---|---|
| 1) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide | 1.1 |
| 2) | 1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N*'-t-butyl-L-prolinamide | 0.58 |
| 3) | 1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]-*N*'-t-butyl-L-prolinamide | 1.5 |
| 4) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(6-bromonaphth-2-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide | 5.8 |
| 5) | (1*S*,3*S*,5*S*)-*N*-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)-ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenyl-butanoyl]-2-azabicyclo[3.3.0]octane-3-*N*'-t-butyl-carboxamide | 0.49 |
| 6) | (1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroisoindole-1-*N*'-t-butylcarboxamide | 1.3 |
| 7) | (1*S*,3*S*,5*S*)-*N*-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-azabicyclo[3.3.0]octane-3-*N*'-t-butylcarboxamide | 2.3 |
| 8) | (1*S*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)-ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenyl-butanoyl]-octahydroisoindole-2-*N*'-t-butylcarboxamide | 0.26 |
| 9) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N*'-t-butylcarboxamide | 1.3 |
| 10) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)-ethan yl-L-valyl)amino-2-hydr xy-4-phenylbutanoyl]-octahydr ind le-2-*N*'-t-butylcarboxamide | 5.7 |
| 11) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)-ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N*'-*iso*-propylcarboxamide | 3.6 |

Table 1 continued

| No. | Compound | $IC_{50}$ nM |
|---|---|---|
| 12) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydro-indole-2-*N'*-t-butylcarboxamide | 30.0 |
| 13) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-phenoxyethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N'*-t-butylcarboxamide | 1.9 |
| 14) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(*N"*-methyl-*N"*-(pyrid-2-ylmethyl)carbamoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide | 25.0 |
| 15) | 1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide | 4.3 |
| 16) | 1-[(2*S*,3*S*)-3-(2-naphth-1-yloxy)ethanoyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide | 1.3 |
| 17) | 1-[(2*S*,3*S*)-3-(2-naphth-1-yloxy)ethanoyl-L-asparaginyl)-amino-2-hydroxy-4-(4'-hydroxy-phenyl)butanoyl]octahydro-indole-2-*N'*-t-butylcarboxamide | 10.0 |
| 18) | 1-[(2*S*,3*S*)-3-(2-naphth-2-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide | 2.8 |

**Example 17**

(*In vitro* cell assay for inhibition of HIV activity)

A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease, such as HIV protease, to generate mature viral proteins required for virus assembly and function. Examples of these viral proteins are reverse transcriptase and p24 core antigen. The following assay measures the level of reverse transcriptase and p24 core antigen present in the growth medium after innoculation of cells with the virus and subsequent treatment with a compound of formula (I). A direct correlation may then be made between the level of reverse transcriptase or the level of p24 core antigen found in the growth medium and the amount of virus produced in the cell. The amount of virus remaining in the cell is a direct indication of the anti-viral activity of the compound tested.

The cells used in this assay were A301 (ALEX) cells, a continuous human T-cell line. The cell growth medium was RPMI-1640 (JR Scientific), supplemented with 5% fetal bovine serum (FBS, JR Scientific). The A301 cells were obtained from the NIH repository. The cells were infected with virus for 3 hours at 37°C in 5% $CO_2$ in air. Cells were also mock-infected at the same time to be used to detect cytotoxicity and to serve as cell controls. Compounds of formula (I) were solubilized in either growth medium or dimethyl sulfoxide, dependent upon solubility. Compounds of formula (I) were then serially diluted in 96-well plates. The final volume of the compounds in the test wells was 100 µL. After the 3 hour infection incubation, the cells were washed three times to remove unabsorbed virus. The infected cells and uninfected cells were then added to appropriate wells of the plates at a

concentration f $3.75 \times 10^4$ in 150 μL. All plates were incubated for 7 days. A 100 μL change of medium and compound was perf rmed on Day 4. At the end of the 7 day incubation, the plates were evaluated for cytotoxicity and p24 core antigen and/or reverse transcriptase (RT) levels. The cytotoxicity of the compounds of formula (I) was evaluated by visual inspection using cell morphology and cell death as criteria. The p24 core antigen level was determined by ELISA using the DuPont p24 Core Antigen test kit according to the method specified by the manufacturer. Virus production was determined by RT levels.

The RT assay was performed as previously described in *Biochem. Pharmacol.* (1987), Vol. 36, pp. 4361-2 whereby an aliquot of supernatant was mixed with 3.2% Triton-X100® to disrupt and inactivate the virus. After a 30 minute incubation period at 37°C, the assay mixture was added to the Triton-X100® supernatant samples and incubated for 1 hour at 37°C. The assay mixture contained 201.0 mmol TRIS buffer (pH 8.0), 20.1 mmol $MgCl_2$, 603.0 mmol KCl, 20 mmol dithiothreitol, 0.02 μg/mL Poly (A) (SIGMA), 0.0023 μg/mL Oligo (dT) 12-18 (PHARMACIA), and 5.1 μmol [$^3$H]thymidine triphosphate (25 Ci/mmol, DuPont New England Nuclear). Aliquots were then spotted on DEAE paper, washed 3 times with a mixture of 5% trichloroacetic acid and 1% pyrophosphate, and fixed in 95% reagent grade ethanol. Radioactivity was measured using a liquid scintillation spectrophotometer, after adding 7 mL of ReadySafe® (Beckman) to each vial. The effective concentration 50% ($EC_{50}$) and effective concentrati n 90% ($EC_{90}$) were defined as the concentration of a compound at which the reverse transcriptase values or p24 levels were reduced by 50% or 90%, respectively, as compared to the reverse transcriptase value or level of p24 obtained from untreated virus control supernatant. These values were determined graphically.

Compounds of formula (I) demonstrated the ability to inhibit HIV production when tested by this assay.

**Example 18**

(*In vitro* cell assay for inhibition of HIV activity)

The following assay measures the level of p24 core antigen present in the cell-free supernatant after innoculation of cells with the virus and subsequent treatment with a compound of formula (I). As described above in Example 15 for reverse transcriptase, a direct correlation may be made between the level of p24 core antigen found in the supernatant and the amount of virus produced in the cell. The amount of virus remaining in the cell is a direct indication of the anti-viral activity of the compound tested.

The cells used were MT-2 cells, a continuous human T-cell line transformed with HTLV-1. The cell growth medium was RPMI-1640 (JR Scientific), supplemented with 5% fetal b vine serum (FBS, JR Scientific). The virus strain ($HTLV\text{-}III_{RF}$) and the MT-2 cells were all obtained from the NIH repository. The cells were infected with virus for 1.5 hours at 37°C in 5% $CO_2$ in air. Cells were als mock-infected at the same time to be used to

detect cytotoxicity and to serve as cell controls. Compounds of formula (I) were solubilized in dimethyl sulfoxide. The compounds were then serially diluted in 96-well plates. The final volume of the compounds in the test wells was 100μl. After the 1.5 hour infection incubation, the cells were washed three times to remove unadsorbed virus. The infected cells and uninfected cells were then added to appropriate wells of the plates at a concentration of $3.75 \times 10^4$ in 150μl. All plates were incubated for 72 hours. At the end of the 72 hours incubation, the plates were evaluated for cytotoxicity and p24 core antigen. The cytotoxicity of the test compounds was evaluated by visual inspection using cell morphology and cell death as criteria. The p24 core antigen level in the supernatants was determined by ELISA using the DuPont p24 Core Antigen test kit according to the method specified by the manufacturer.

The effective concentration 50% ($EC_{50}$) and effective concentration 90% ($EC_{90}$) were defined as the concentration of a compound of formula (I) at which the p24 levels were reduced by 50% or 90%, respectively, as compared to the level of p24 obtained from untreated virus control supernatant. These values were determined graphically.

Compounds of formula (I) demonstrated the ability to inhibit the production of HIV when tested by this assay as shown in the below table.

TABLE 2

| No. | Compound | $EC_{50}/EC_{90}$ nM |
|---|---|---|
| 1) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide | 5-38/35-140 10 determ'ns |
| 2) | 1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide | 131/360 |
| 3) | 1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)-amino-2-hydroxy-4-phenylbutanoyl]-*N'*-t-butyl-L-prolinamide | 145/540 |
| 4) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(6-bromonaphth-2-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N'*-t-butylcarboxamide | 65/140 |
| 5) | (1*S*,3*S*,5*S*)-*N*-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)-ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenyl-butanoyl]-2-azabicyclo[3.3.0]octane-3-*N'*-t-butyl-carboxamide | 5.3-15/35-37 4 determ'ns |
| 6) | (1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroisoindole-1-*N'*-t-butylcarboxamide | 47/153 |
| 7) | (1*S*,3*S*,5*S*)-*N*-[(2*S*,3*S*)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-azabicyclo[3.3.0] ctane-3-*N'*-t-butylcarboxamide | 78/151 |
| 8) | (1*S*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)-ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenyl-butanoyl]-octahydroisoindole-2-*N'*-t-butylcarboxamide | 18/144 |

Table 2 continued

| No. | Compound | $EC_m/EC_n$ nM |
|---|---|---|
| 9) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N*'-t-butylcarboxamide | 7-26/23-110 6 determ'ns |
| 10) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)-ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N*'-t-butylcarboxamide | 7-36/33-120 4 determ'ns |
| 11) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)-ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N*'-*iso*-propylcarboxamide | 6-110/35-160 5 determ'ns |
| 12) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydro-indole-2-*N*'-t-butylcarboxamide | 57/530 |
| 13) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-phenoxyethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N*'-t-butylcarboxamide | 82/420 |
| 14) | (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(*N*'-methyl-*N*'-(pyrid-2-ylmethyl)carbamoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide | 240/2,200 |
| 15) | 1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-*N*'-t-butyl-L-prolinamide | 500/620 |
| 16) | 1-[(2*S*,3*S*)-3-(2-naphth-1-yloxy)ethanoyl-L-asparaginyl)-amino-2-hydroxy-4-phenyl-butanoyl]-*N*'-t-butyl-L-prolinamide | 90-103/140-150 2 determ'ns |
| 17) | 1-[(2*S*,3*S*)-3-(2-naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-(4'-hydroxy-phenyl)butanoyl]octahydroindole-2-*N*'-t-butyl carboxamide | 360/1,420 |
| 18) | 1-[(2*S*,3*S*)-3-(2-naphth-2-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-*N*'-t-butyl-*L*-prolinamide | 146/534 |

**Example 19**

(cytotoxicity)

At the same time the supernatants were removed for p24 determinations in the above assay (see Example 18), the cell control wells were read for compound toxicity.

At each concentration of compound, the number of live cells in the control wells (no virus infection) were read and the number compared to the cell control wells (no compound and no virus). The following rating scale was used:

0 = no fewer cells than in the cell control
1 = 0-25% fewer cells than in the cell control
2 = 25-50% fewer cells than in the cell control
3 = 50-75% fewer cells than in the cell control
4 = 75-100% fewer cells than in the cell control

Partial toxicity was defined as the lowest concentration of compound tested at which there was any visual reduction in cell growth. Complete toxicity was

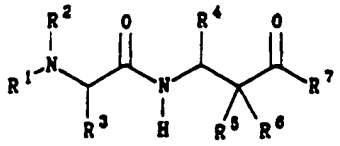
defined as the lowest concentration f compound tested at which a score of "4" was given for toxicity. For compound (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydroindole-2-*N*'-t-butylcarboxamide, the partial toxicity was 10 $\mu$M and the complete toxicity was >10 $\mu$M.

*****

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

**WHAT IS CLAIMED IS:**

1. A compound of formula (I):



(I)

wherein:

$R^1$ is alkoxycarbonyl, aralkoxycarbonyl, optionally substituted aralkanoyl, optionally substituted aroyl, optionally substituted heterocyclylcarbonyl, optionally substituted aryloxyalkanoyl, optionally substituted carbamoyl or optionally substituted heterocyclyloxyalkanoyl;

$R^2$ is hydrogen;

$R^3$ is alkyl optionally substituted by hydroxy, carbamoyl, monoalkylcarbamoyl, or dialkylcarbamoyl;

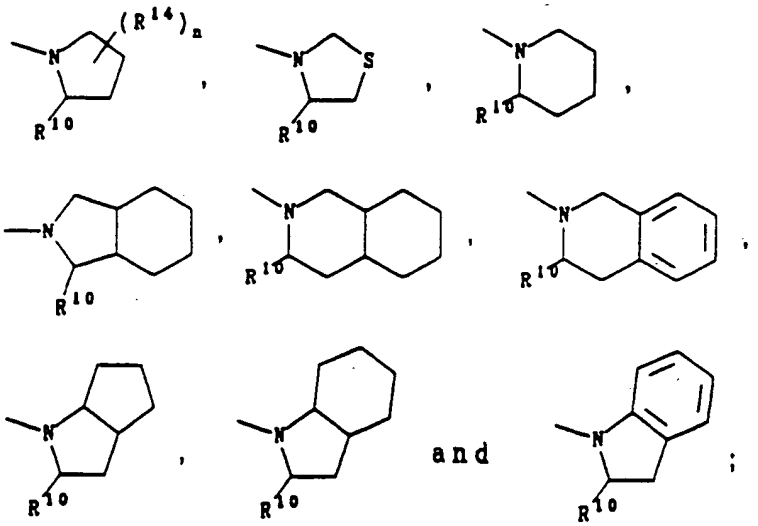
$R^4$ is optionally substituted aryl or optionally substituted aralkyl;

$R^5$ is hydrogen;

$R^6$ is hydroxy; or

$R^5$ and $R^6$ together form oxo; and

$R^7$ is selected from the group consisting of:



wherein

n is 0, 1 or 2;

each $R^{14}$ is independently hydroxy, alkyl, alkoxy or phenyl; and

$R^{10}$ is alkoxycarbonyl or opti nally substitut d carbamoyl;

as a single stere isomer or as a mixture thereof; or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein the carb n to which $R^4$ is attached

is in the *S*-configuration and the carbon to which $R^5$ and $R^6$ are attached is in the *S*-configuration; and wherein

$R^1$ is aralkoxycarbonyl, optionally substituted aryloxyalkanoyl, optionally substituted carbamoyl or optionally substituted heterocyclylcarbonyl;

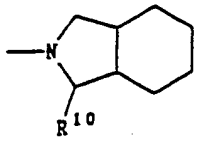
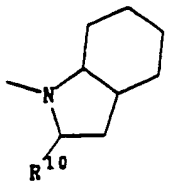
$R^3$ is alkyl optionally substituted by carbamoyl;

$R^4$ is optionally substituted aralkyl;

$R^5$ is hydrogen;

$R^6$ is hydroxy; and

$R^7$ is selected from the group consisting of:


and


wherein

$R^{10}$ is monoalkyl carbamoyl.

3. A compound of Claim 2 wherein:

$R^1$ is optionally substituted aryloxyalkanoyl;

$R^3$ is 1-methylethyl or methyl substituted by carbamoyl; and

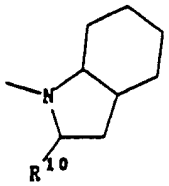
$R^4$ is benzyl.

4. A compound of Claim 3 wherein:

$R^1$ is 2-(naphth-1-yloxy)ethanoyl;

$R^3$ is methyl substituted by carbamoyl; and

$R^7$ is



wherein $R^{10}$ is *N*-*t*-butylcarbamoyl;

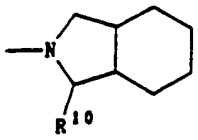
one of the steroisomers of which is named, (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N'*-*t*-butylcarboxamide.

5. A compound of Claim 3 wherein:

$R^1$ is 2-(naphth-1-yloxy)ethanoyl;

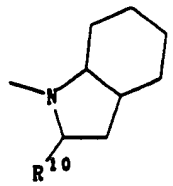
$R^3$ is methyl substituted by carbamoyl; and

$R^7$ is



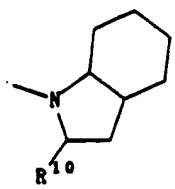
wherein $R^{10}$ is *N*-t-butylcarbamoyl;
two of the stereoisomers of which are named, (1*S*,3a*R*,7a*S*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroisoindole-1-*N'*-t-butylcarboxamide, and (1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroisoindole-1-*N'*-t-butylcarboxamide.

6. A compound of Claim 3 wherein:
$R^1$ is 2-(naphth-1-yloxy)ethanoyl;
$R^3$ is 1-methylethyl; and
$R^7$ is



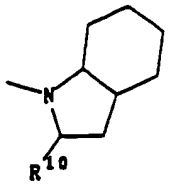
wherein $R^{10}$ is *N*-t-butylcarbamoyl or *N*-*iso*-propylcarbamoyl;
two of the stereoisomers of which are named, (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N'*-t-butylcarboxamide, and (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N'*-*iso*-propylcarboxamide.

7. A compound of Claim 3 wherein:
$R^1$ is 2-phenoxyethanoyl;
$R^3$ is methyl substituted by carbamoyl;
$R^7$ is



wherein $R^{10}$ is *N*-t-butylcarbamoyl;
one of the stereoisomers of which is named, (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(2-phenoxyethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N'*-t-butylcarboxamide.

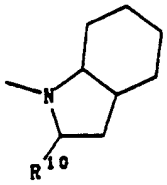
8. A compound of Claim 3 wherein:
$R^1$ is 2-(naphth-1-yloxy)ethanoyl;
$R^3$ is methyl substitut d by carbamoyl;
$R^7$ is



wherein $R^{10}$ is *N*-*t*-butylcarboxamide;
one of the stereoisomers of which is named, (1*S*,3*S*,5*S*)-*N*-[(2*S*,3*S*)-3-(2-(naphth-1-yloxy)ethanoyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-2-azabicyclo[3.3.0]octane-3-*N*'-*t*-butylcarboxamide.

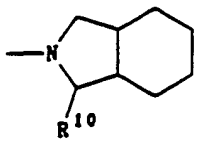
9. A compound of Claim 2 wherein:
$R^1$ is optionally substituted heterocyclylcarbonyl;
$R^3$ is 1-methylethyl or methyl substituted by carbamoyl; and
$R^4$ is benzyl.

10. A compound of Claim 9 wherein:
$R^1$ is quinol-2-ylcarbonyl;
$R^3$ is methyl substituted by carbamoyl; and
$R^7$ is



wherein $R^{10}$ is *N*-*t*-butylcarbamoyl;
one of the stereoisomers of which is named, (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindol-2-*N*'-*t*-butylcarboxamide.

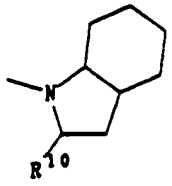
11. A compound of Claim 9 wherein:
$R^1$ is quinol-2-ylcarbonyl;
$R^3$ is methyl substituted by carbamoyl; and
$R^7$ is



wherein $R^{10}$ is *N*-*t*-butylcarbamoyl;

one of the stereoisomers of which is named, (1*S*,3a*S*,7a*R*)-2-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]octahydro-isoindole-1-*N'*-t-butylcarboxamide.

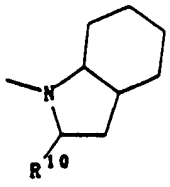
12. A compound of Claim 9 wherein:
$R^1$ is quinol-2-ylcarbonyl;
$R^3$ is 1-methylethyl; and
$R^7$ is



wherein $R^{10}$ is *N*-t-butylcarbamoyl;
one of the stereoisomers of which is named, (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(quinol-2-ylcarbonyl-L-valyl)amino-2-hydroxy-4-phenylbutanoyl]-octahydroindole-2-*N'*-t-butylcarboxamide.

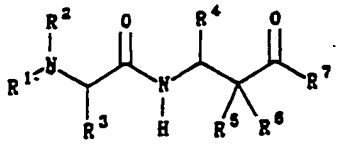
13. A compound of Claim 2 wherein:
$R^1$ is optionally substituted carbamoyl;
$R^3$ is 1-methylethyl or methyl substituted by carbamoyl; and
$R^4$ is benzyl.

14. A compound of Claim 13 wherein:
$R^1$ is *N*-methyl-*N*-(pyrid-2-ylmethyl)carbamoyl;
$R^3$ is 1-methylethyl; and
$R^7$ is



wherein $R^{10}$ is *N*-t-butylcarbamoyl;
one of the stereoisomers of which is named, (2*S*,3a*S*,7a*S*)-1-[(2*S*,3*S*)-3-(*N*"-methyl-*N*"-(pyrid-2-ylmethyl)carbamoyl-L-valyl)amino-2-hydroxy-4-phenyl-butanoyl]octahydroindole-2-*N'*-t-butylcarboxamide.

15. Use of a compound of formula (I):



(I)

wherein:

$R^1$ is alkoxycarbonyl, aralkoxycarbonyl, optionally substituted aralkanoyl, optionally substituted aroyl, optionally substituted heterocyclylcarbonyl, optionally substituted aryloxyalkanoyl, optionally substituted carbamoyl or optionally substituted heterocyclyloxyalkanoyl;

$R^2$ is hydrogen;

$R^3$ is alkyl optionally substituted by hydroxy, carbamoyl, monoalkylcarbamoyl, or dialkylcarbamoyl;

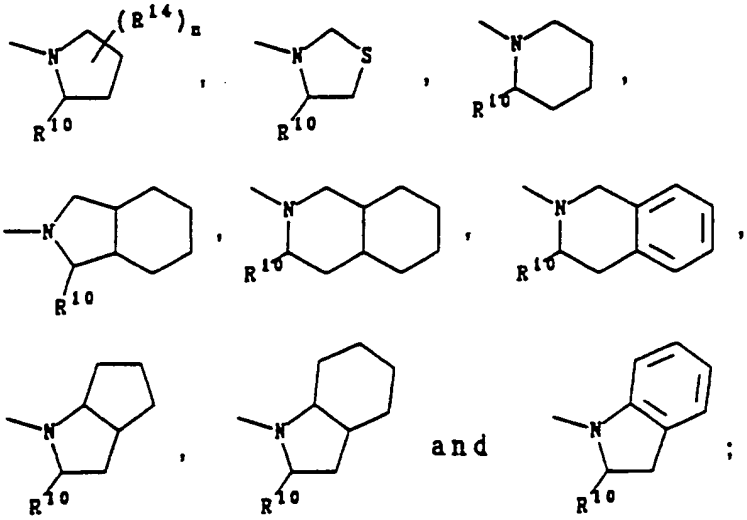
$R^4$ is optionally substituted aryl or optionally substituted aralkyl;

$R^5$ is hydrogen;

$R^6$ is hydroxy; or

$R^5$ and $R^6$ together form oxo; and

$R^7$ is selected from the group consisting of:



wherein

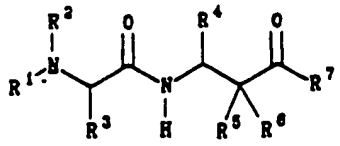
n is 0, 1 or 2;

each $R^{14}$ is independently hydroxy, alkyl, alkoxy or phenyl; and

$R^{10}$ is alkoxycarbonyl or optionally substituted carbamoyl;

as a single stereoisomer or as a mixture thereof; or a pharmaceutically acceptable salt thereof, for inhibiting HIV protease in a mammal.

16. A pharmaceutical composition useful for the inhibition of HIV protease in mammals, which composition comprises a therapeutically effective amount of a compound of formula (I):



(I)

wherein:

$R^1$ is alkoxycarbonyl, aralkoxycarbonyl, optionally substituted aralkanoyl, optionally substituted aroyl, optionally substituted heterocyclylcarbonyl, optionally substituted aryloxyalkanoyl, optionally substituted carbamoyl or optionally substituted heterocyclyloxyalkanoyl;

$R^2$ is hydrogen;

$R^3$ is alkyl optionally substituted by hydroxy, carbamoyl, monoalkylcarbamoyl, or dialkylcarbamoyl;

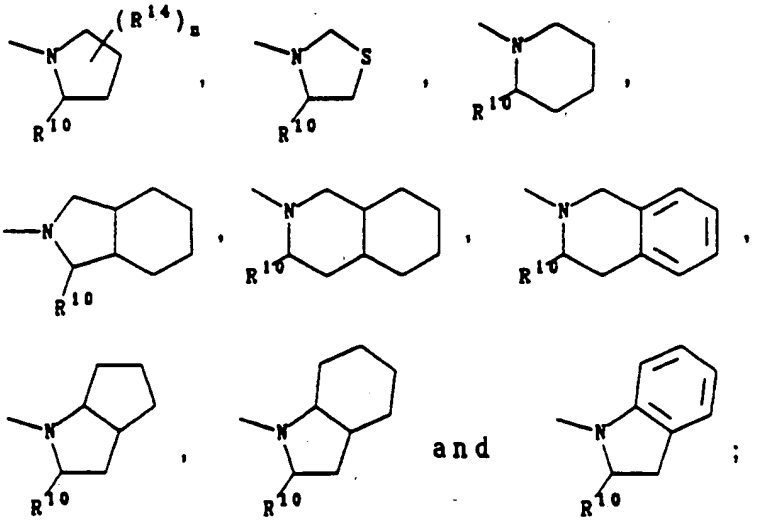
$R^4$ is optionally substituted aryl or optionally substituted aralkyl;

$R^5$ is hydrogen;

$R^6$ is hydroxy; or

$R^5$ and $R^6$ together form oxo; and

$R^7$ is selected from the group consisting of:



wherein

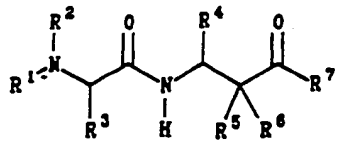
n is 0, 1 or 2;

each $R^{14}$ is independently hydroxy, alkyl, alkoxy or phenyl; and

$R^{10}$ is alkoxycarbonyl or optionally substituted carbamoyl;

as a single stereoisomer or as a mixture thereof; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

17. A process for the preparation of a compound of formula (I):



(I)

wherein:

$R^1$ is alkoxycarbonyl, aralkoxycarbonyl, optionally substituted aralkanoyl, optionally substituted aroyl, optionally substituted heterocyclylcarbonyl, optionally substituted aryloxyalkanoyl, optionally substituted carbamoyl or optionally substituted heterocyclyloxyalkanoyl;

$R^2$ is hydrogen;

$R^3$ is alkyl optionally substituted by hydroxy, carbamoyl, monoalkylcarbamoyl, or dialkylcarbamoyl;

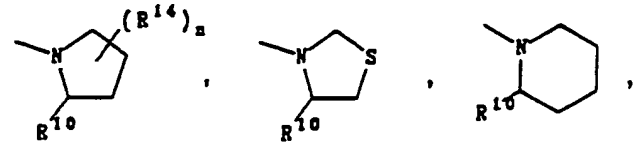
$R^4$ is optionally substituted aryl or optionally substituted aralkyl;

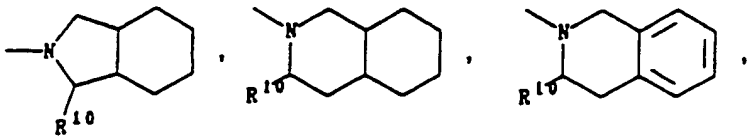
$R^5$ is hydrogen;

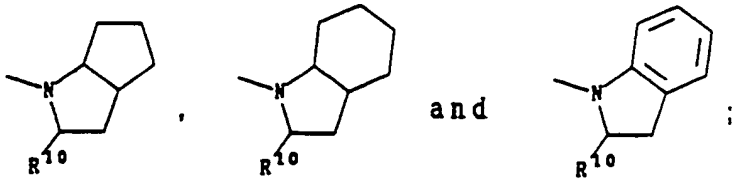
$R^6$ is hydroxy; or

$R^5$ and $R^6$ together form oxo; and

$R^7$ is selected from the group consisting of:







wherein

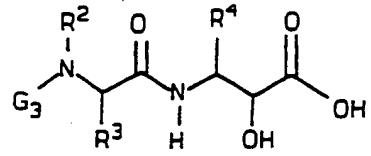
n is 0, 1 or 2;

each $R^{14}$ is independently hydroxy, alkyl, alkoxy or phenyl; and

$R^{10}$ is alkoxycarbonyl or optionally substituted carbamoyl;

as a single stereoisomer or as a mixture thereof; or a pharmaceutically acceptable salt thereof, which comprises

a) reacting a compound of the formula

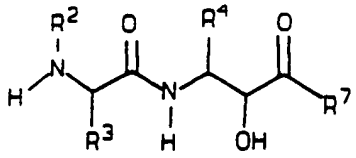


wherein $G_3$ is an amino-protecting gr up selected from the group consisting of t-butoxycarbonyl, 2-(naphth-1-yloxy)ethan yl and benzyloxycarbonyl and $R^2$, $R^3$, and $R^4$ are as defined above, with a compound of the formula

$$H - R^7$$

wherein $R^7$ is as defined above, to form a compound of formula (I) wherein $G_3$ is as defined above; or

b) treating a compound of the formula

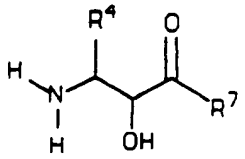


wherein $R^2$, $R^3$, $R^4$, and $R^7$ are as defined above, with a compound of the formula

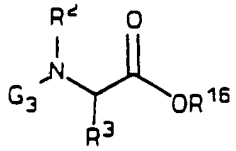
$$R^1 - OH$$

wherein $R^1$ is as defined above, to form a compound of formula (I); or

c) reacting a compound of the formula



wherein $R^4$ and $R^7$ are as defined above, with a compound of the formula



wherein $G_3$, $R^2$, and $R^3$ are as defined above and $R^{16}$ is hydrogen or p-nitrophenyl, to form a compound of formula (I) wherein $G_3$ is as defined above; or

d) oxidizing a compound of formula (I) wherein $R^5$ is hydrogen and $R^6$ is hydroxy, to form a compound of formula (I) wherein $R^5$ and $R^6$ together form oxo; or

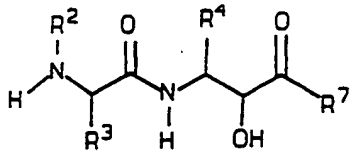
e) converting a compound of formula (I) to a pharaceutically acceptable salt thereof; or

f) converting a pharmaceutically acceptable salt of a compound of formula (I) to the corresponding free compound f formula (I); or

g) converting a pharmaceutically acceptable salt f a compound of formula (I) to another pharmaceutically acceptable salt of a compound of formula (I).

18. The process of Claim 17, step a) or c), which process further comprises

a) catalytically hydrogenating a compound of formula (I) wherein $G_3$ is an amino-protecting group selected from the group c nsisting of t-butoxycarbonyl, 2-(naphth-1-yloxy)ethanoyl and benzyloxycarbonyl and $R^2$, $R^3$, $R^4$, and $R^7$ are as defined above, to form a compound of the formula



followed by

b) treating a compound of formula (L) wherein $R^2$, $R^3$, $R^4$, and $R^7$ are as defined above, with a compound of the formula

$$R^1 - OH$$

wherein $R^1$ is as defined above, to form a compound of formula (I); optionally followed by

c) oxidizing a compound of formula (I) wherein $R^5$ is hydrogen and $R^6$ is hydroxy, to form a compound of formula (I) wherein $R^5$ and $R^6$ together form oxo; or

d) converting a compound of formula (I) to a pharaceutically acceptable salt thereof; or

e) converting a pharmaceutically acceptable salt of a compound of formula (I) to the corresponding free compound of formula (I); or

f) converting a pharmaceutically acceptable salt of a compound of formula (I) to another pharmaceutically acceptable salt of a compound of formula (I).

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/10772

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D207/16; C07D209/42; C07D209/44; C07D209/52
C07D211/60; C07D217/26; C07D277/06; A61K31/40

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07D ; A61K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| P,X<br>P,Y | EP,A,0 498 680 (SANKYO COMPANY, LTD.)<br>12 August 1992<br>* Table 1 *<br>see claims 1-26,39,42-47 | 1,15-18<br>2-14 |
| Y | EP,A,0 346 847 (F. HOFFMANN-LA ROCHE AG)<br>20 December 1989<br>* entire document *<br>see claims 1-25 | 1-18 |
| P,Y | J. MED. CHEM.<br>vol. 35, no. 7, 1992,<br>pages 1318 - 1320<br>T.F. TAM ET AL. 'Intriguing structure-activity relations underlie the potent inhibition of HIV protease by norstatine-based peptides'<br>* entire document * | 1-18 |

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 06 MAY 1993 | 25. 05. 93 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT FFICE | HERZ C.P. |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| Y | J. MED. CHEM.<br>vol. 20, no. 47, 1977,<br>pages 510 - 515<br>R. NISHIZAWA ET AL. 'Synthesis and Structure-Activity Relationships of Bestatin Analogues, Inhibitors of Aminopeptidase B'<br>* entire document * | 1-16 |
| Y | CHEM. PHARM. BULL.<br>vol. 39, no. 11, 1991,<br>pages 3088 - 3090<br>T. MIMOTO ET AL. 'KNI-102, a novel tripeptide HIV protease inhibitor containing allophenylnorstatine as a transition-state mimic'<br>* entire document * | 1-16 |
| Y | CHEM. PHARM. BULL.<br>vol. 39, no. 9, 1991,<br>pages 2465 - 2467<br>T. MIMOTO ET AL. 'Rational design and synthesis of a novel class of active site-targeted HIV protease inhibitors containing a hydroxymethylcarbonyl isostere. Use of Phenylnorstatine or allophenylnorstatine as a transition-state mimic'<br>* entire document * | 1-16 |

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9210772
SA 68307

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/05/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A-0498680 | 12-08-92 | AU-A- | 1081292 | 13-08-92 |
| | | CA-A- | 2060844 | 09-08-92 |
| EP-A-0346847 | 20-12-89 | AU-B- | 624144 | 04-06-92 |
| | | AU-A- | 3613089 | 14-12-89 |
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| | | US-A- | 5157041 | 20-10-92 |